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(54) Title: HEPATITIS B VIRAL VARIANTS WITH REDUCED SUSCEPTIBILITY TO NUCLEOSIDE ANALOGS AND USES THEREOF

(57) Abstract: The present invention relates generally to viral variants exhibiting reduced sensitivity to particular agents and/or reduced interactivity with immunological reagents. More particularly, the present invention is directed to hepatitis B virus (HBV) variants exhibiting complete or partial resistance to nucleoside or nucleotide analogs and/or reduced interactivity with antibodies to viral surface components including reduced sensitivity to these antibodies. The present invention further contemplates assays for detecting such viral variants, which assays are useful in monitoring anti-viral therapeutic regimens and in developing new or modified vaccines directed against viral agents and in particular HBV variants. The present invention also contemplates the use of the viral variants to screen for and/or develop or design agents capable of inhibiting infection, replication and/or release of the virus.



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## VIRAL VARIANTS, DETECTION AND USE

### BACKGROUND OF THE INVENTION

#### 5 FIELD OF THE INVENTION

The present invention relates generally to viral variants exhibiting reduced sensitivity to particular agents and/or reduced interactivity with immunological reagents. More particularly, the present invention is directed to hepatitis B virus (HBV) variants exhibiting  
10 complete or partial resistance to nucleoside or nucleotide analogs and/or reduced interactivity with antibodies to viral surface components including reduced sensitivity to these antibodies. The present invention further contemplates assays for detecting such viral variants, which assays are useful in monitoring anti-viral therapeutic regimens and in developing new or modified vaccines directed against viral agents and in particular HBV  
15 variants. The present invention also contemplates the use of the viral variants to screen for and/or develop or design agents capable of inhibiting infection, replication and/or release of the virus.

#### DESCRIPTION OF THE PRIOR ART

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Bibliographic details of the publications referred to in this specification are also collected at the end of the description.

The reference to any prior art in this specification is not, and should not be taken as, an  
25 acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in any country.

Hepatitis B virus (HBV) can cause debilitating disease conditions and can lead to acute liver failure. HBV is a DNA virus which replicates *via* an RNA intermediate and utilizes  
30 reverse transcription in its replication strategy (Summers and Mason, *Cell* 29: 403-415, 1982). The HBV genome is of a complex nature having a partially double-stranded DNA

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Whilst these agents are highly effective in inhibiting HBV DNA synthesis, there is the potential for resistant mutants of HBV to emerge during long term antiviral chemotherapy. In patients on prolonged LMV therapy, key resistance mutations are selected in the rt domain within the polymerase at rtM204I/V +/- rtL180M as well as other mutations. The nomenclature used for the polymerase mutations is in accordance with that proposed by Stuyver *et al.*, 2001, *supra*. LMV is a nucleoside analog that has been approved for use against chronic HBV infection. LMV is a particularly potent inhibitor of HBV replication and reduces HBV DNA titres in the sera of chronically infected patients after orthotopic liver transplantation (OLT) by inhibiting viral DNA synthesis. LMV monotherapy seems unlikely to be able to control HBV replication in the longer term. This is because emergence of LMV-resistant strains of HBV seems almost inevitable during monotherapy.

Adefovir dipivoxil (ADV: formerly, bis-pom PMEA) is an orally available prodrug of the acyclic deoxyadenosine monophosphate analog adefovir (formerly, PMEA) (Figure 2). ADV is also a potent inhibitor of HBV replication and has recently been given FDA approval for use against chronic HBV infection. Adefovir dipivoxil differs from other agents in this class in that it is a nucleotide (vs. nucleoside) analog and as such bypasses the first phosphorylation reaction during drug activation. This step is often rate-limiting. Adefovir dipivoxil has demonstrated clinical activity against both wild-type and lamivudine-resistant strains of HBV and is currently in phase III clinical Testing (Gilson *et al.*, *J Viral Hepat* 6: 387-395, 1999; Perrillo *et al.*, *Hepatology* 32: 129-134, 2000; Peters *et al.*, *Transplantation* 68: 1912-1914, 1999; Benhamou *et al.*, *Lancet* 358: 718-723, 2001). During phase II studies a 30 mg daily dose of adefovir dipivoxil resulted in a mean 4 log<sub>10</sub> decrease in viremia over 12 weeks (Heathcote *et al.*, *Hepatology* 28: A620, 1998).

ADV is a substituted acyclic nucleoside phosphonate. This class of compounds also includes tenofovir disoproxil fumarate (also referred to as tenofovir DF, or tenofovir, or (TFV) or 9-R-(2-phosphonomethoxypropyl)adenine (PMPA) and is marketed as Viread by Gilead sciences).

## SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word “comprise”, or variations such as “comprises” or “comprising”, will be understood to imply the  
5 inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

Nucleotide and amino acid sequences are referred to by a sequence identifier number (SEQ ID NO:). The SEQ ID NOs: correspond numerically to the sequence identifiers <400>1  
10 (SEQ ID NO:1), <400>2 (SEQ ID NO:2), etc. A summary of the sequence identifiers is provided in Table 1. A sequence listing is provided after the claims.

Specific mutations in an amino acid sequence are represented herein as “Xaa<sub>1</sub>nXaa<sub>2</sub>” where Xaa<sub>1</sub> is the original amino acid residue before mutation, n is the residue number and  
15 Xaa<sub>2</sub> is the mutant amino acid. The abbreviation “Xaa” may be the three letter or single letter (i.e. “X”) code. An “rt” before “Xaa<sub>1</sub>nXaa<sub>2</sub>” means “reverse transcriptase”. An “s” means an envelope gene. The amino acid residues for HBV DNA polymerase are numbered with the residue methionine in the motif Tyr Met Asp Asp (YMDD) being residue number 204 (Stuyver *et al.*, *Hepatology* 33: 751-757, 2001). The amino acid  
20 residues for hepatitis B virus surface antigen are number according to Norder *et al.* (*J. Gen. Virol.* 74: 341-1348, 1993). Both single and three letter abbreviations are used to define amino acid residues and these are summarized in Table 2.

In accordance with the present invention, the selection of HBV variants is identified in  
25 patients (Patient A, C and D) with chronic HBV infection treated with ADV and liver transplant patients (Patients B and E) treated with both ADV and LMV post-OLT or ADV post-transplant. HBV variants from Patients F, G and H were also identified following similar treatments. Variants of HBV are identified during ADV or combination ADV and LMV treatment with mutations in the HBV DNA polymerase gene which reduce the  
30 sensitivity of HBV to this nucleoside analog. Consequently, HBV rt variants are contemplated which are resistant to, or which exhibit reduced sensitivity to, ADV,



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comprises a mutation in an overlapping open reading frame in its genome in a region defined by one or more of domains F and G and domain A through to E of HBV DNA polymerase.

- 5 Another aspect of the present invention provides an isolated HBV variant comprising a nucleotide mutation in the S gene resulting in at least one amino acid addition, substitution and/or deletion to the surface antigen and which exhibits decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV,  
 10 TFV and FTC and LMV, or ADV and FTC and LMV and TFV, ADV and LMV and FTC, and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combinations thereof.

Useful mutants in the rt region include, in one embodiment, rtS21A, rtL122F, rtN124H,  
 15 rtH126R, rtT28N, rtP130Q, rtD131N and rtY135C; in another embodiment, rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M; in a further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and  
 20 rtV214A; and in yet another embodiment, rtH90D and rtL/F108L; and in still a further embodiment, rtL157L/M, rtA181V and rtV207I and in yet a further embodiment, rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K; and in another embodiment, rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H or a combination thereof or an equivalent mutation.

25 Other HBV variants are also contemplated with mutations in rt at rtK32, rtN33, rtP34, rtH35 and rtT37 (these are upstream of the F domain of the DNA polymerase), rtP59, rtK60, rtF61, rtA62 and rtV63 (these are located between the F and A domains), rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91 (these are located within the A domain and  
 30 the region immediately prior to and following), rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184 (these are located in the B domain), rtM204 and rtY203 (these

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Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
 M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
 L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 5 T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
 P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
 10 S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
 Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
 K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 15 H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
 M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
 G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
 V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion.

20

Reference above to "deletion" means that the first mentioned amino acid before the residue number has been deleted.

Useful mutations in the S gene include, in one embodiment, sP120T, sM125T and  
 25 sT127A; in another embodiment, T118R, sM133T, sF134V sI195M, sS207R and  
 sY225Y/C; in a further embodiment, sS126T, sM133L/M, sS143S/T, sD144A sG145A  
 and sW172Stop; in yet a further embodiment, sN40S, sC69 Stop, sM75I, sL88P, sT118A,  
 sW182stop, sW196L, sY206H and sY225F; and in yet another embodiment, sI81M and  
 sP214Q; and in still another embodiment, sF83S, sL173F and sW199L; and in still yet  
 30 another embodiment, sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L  
 and sY221C; and in yet another embodiment, sC69Stop/C, sC76Y sI110V/I, sY134N,

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derivative form thereof or its chemical equivalent and one or more pharmaceutically acceptable carriers and/or diluents.

Yet another aspect of the present invention provides a use of the aforementioned  
5 composition or a variant HBV comprising a nucleotide mutation in a gene encoding a DNA polymerase resulting in at least one amino acid addition, substitution and/or deletion to the DNA polymerase and a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV  
10 and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combination thereof in the manufacture of a medicament for the treatment and/or prophylaxis of hepatitis B virus infection.

15 The present invention also contemplates a method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside or nucleotide analog or other anti-HBV agents or by isolating DNA or corresponding mRNA from the HBV and screening for a mutation in the nucleotide sequence encoding the DNA polymerase wherein the presence of the following mutations in the rt region: in one embodiment, rtS21A, rtL122F, rtN124H, rtH126R, rtT28N, rtP130Q, rtD131N and rtY135C; in another embodiment,  
20 rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M; in a further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and  
25 rtV214A; in still another embodiment, rtH90D and rtL/F108L, in even yet another embodiment, rtL157L/M, rtA181V and rtV207I; in still yet another embodiment, rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K; in another embodiment, rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H; in a further embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37; in yet another  
30 embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63; in still another embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91; in even yet another embodiment, rtP177,

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variant HBV. The detection of HBV or its components in cells, cell lysates, cultured supernatant fluid and bodily fluid may be by any convenient means including any nucleic acid-based detection means, for example, by nucleic acid hybridization techniques or *via* one or more polymerase chain reactions (PCRs). The term "bodily fluid" includes any fluid  
5 derived from the blood, lymph, tissue or organ systems including serum, whole blood, biopsy and biopsy fluid, organ explants and organ suspension such as liver suspensions.

Another aspect of the present invention is directed to a variant HBV comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution,  
10 addition and/or deletion or a truncation compared to a surface antigen from a reference or wild type HBV and wherein an antibody generated to the reference or wild type surface antigen exhibits an altered immunological profile relative to the HBV variant. One altered profile includes a reduced capacity for neutralizing the HBV. More particularly, the surface antigen of the variant HBV exhibits an altered immunological profile compared to  
15 a pre-treatment HBV where the variant HBV is selected for by a nucleoside or nucleotide analog or other anti-HBV agents of the HBV DNA polymerase. The variant HBV of this aspect of the invention may also comprise a nucleotide sequence comprising a single or multiple nucleotide substitution, addition and/or deletion compared to a pre-treatment HBV.

20

The present invention extends to an isolated HBsAg or a recombinant form thereof or derivative or chemical equivalent thereof corresponding to the variant HBV. Generally, the HBsAg or its recombinant or derivative form or its chemical equivalent comprises an amino acid sequence with a single or multiple amino acid substitution, addition and/or  
25 deletion or a truncation compared to an HBsAg from a reference HBV and wherein an antibody directed to a reference HBV exhibits an altered immunological profile to an HBV carrying said variant HBsAg. In one embodiment, the altered immunological profile comprises a reduction in the ability to neutralize the variant HBV.

30 Another aspect of the present invention contemplates a method for detecting an agent which exhibits inhibitory activity to an HBV by generating a genetic construct comprising

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cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed genetic material and/or assembled and/or been released in the presence of the agent.

- 5 In an alternative embodiment, the present invention also contemplates a method for detecting an agent which exhibits inhibitory activity to an HBV polymerase in an *in vitro* polymerase assay. The HBV polymerase activity can be examined using established assays (Gaillard *et al.*, *Antimicrob Agents Chemother.* 46(4): 1005-1013, 2002; Xiong *et al.*, *Hepatology.* 28(6): 1669-73, 1998). The HBV polymerase may be a wild-type or reference  
10 HBV polymerase or mutant HBV polymerase.

- The identification of viral variants enables the production of vaccines comprising particular recombinant viral components such as polymerases or envelope genes PreS1, PreS2, S encoding for L, M, S proteins as well as therapeutic vaccines comprising  
15 defective HBV variants. Rational drug design may also be employed to identify or generate therapeutic molecules capable of interacting with a polymerase or or envelope genes PreS1, PreS2, S encoding for L, M, S proteins or other component of the HBV. Such drugs may also have diagnostic potential. In addition, defective HBV variants may also be used as therapeutic compositions to generate an immune response against the same, similar  
20 or homologous viruses. Alternatively, antibodies generated to the HBV variants or surface components thereof may be used in passive immunization of subjects against infection by HBV variants or similar or homologous viruses. Furthermore, agents such as nucleoside or nucleotide analogs, RNAi or siRNA molecules, antisense or sense oligonucleotides, chemical or proteinaceous molecules having an ability to down-regulate the activity of a  
25 component of HBV and inhibit replication, maintenance, infection, assembly or release are contemplated by the present invention.

A summary of the abbreviations used throughout the subject specification are provided in Table 3.

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SEQUENCE ID NO:	DESCRIPTION
24	HBsAg Trans of 2 (Figure 6)
25	HBsAg Trans of 3 (Figure 6)
26	HBsAg Trans of 4(Figure 6)
27	S0 (Figure 7)
28	S6 (Figure 7)
29	S8 (Figure 7)
30	S12 (Figure 7)
31	S15 (Figure 7)
32	Pol Trans S0 (Figure 8)
33	Pol Trans S6 (Figure 8)
34	Pol Trans S8 (Figure 8)
35	Pol Trans S12 (Figure 8)
36	Pol Trans S15 (Figure 8)
37	HBsAg Trans of S0 (Figure 9)
38	HBsAg Trans of S6 (Figure 9)
39	HBsAg Trans of S8 (Figure 9)
40	HBsAg Trans of S12 (Figure 9)
41	HBsAg Trans of S15 (Figure 9)
42	Nucleotide sequence Patient C (Figure 10)
43	POL Trans of Patient C (Figure 11)
44	HBsAg Trans of Patient C ( Figure 12)
45	Nucleotide sequence of Patient D (Figure 13)
46	Pol Trans of Patient D (Figure 14)
47	HBsAg Trans of Patient D (Figure 15)
48	Nucleotide sequence of Patient E (Figure 16)
49	Pol Trans of Patient E (Figure 17)
50	HBsAg Trans of Patient E (Figure 18)
51	Nucleotide sequence of Patient F (Figure 20)
52	Deduced sequence of DNA polymerase of Patient F (Figure 21)

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TABLE 2

*Single and three letter amino acid abbreviations*

Amino Acid	Three-letter Abbreviation	One-letter symbol
Alanine	Ala	A
Arginine	Arg	R
Asparagine	Asn	N
Aspartic acid	Asp	D
Cysteine	Cys	C
Glutamine	Gln	Q
Glutamic acid	Glu	E
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Leucine	Leu	L
Lysine	Lys	K
Methionine	Met	M
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	The	T
Tryptophan	Trp	W
Tyrosine	-Tyr	Y
Valine	Val	V
Any residue	Xaa	X

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** is a diagrammatic representation showing the partially double stranded DNA HBV genome showing the overlapping open reading frames encoding surface (S), core  
5 (C), polymerase (P) and X gene.

**Figure 2** is a diagrammatic representation of the chemical structure of ADV.

**Figure 3** is a diagrammatic representation of a computer system for determining the  
10 potency value ( $P_A$ ) of a variant HBV.

**Figure 4** is a representation showing comparison of the HBV nucleotide sequence encoding the catalytic region of the polymerase gene in sequential samples from Patient A during ADV treatment.  
15

**Figure 5** is a representation showing comparison of the deduced amino acid sequence of the catalytic region of the polymerase gene in sequential samples from Patient A during ADV therapy.

**Figure 6** is a representation showing comparison of the deduced amino acid sequence of the envelope gene in sequential samples from Patient A during ADV therapy.  
20

**Figure 7** is a representation showing comparison of the HBV nucleotide sequence encoding the catalytic region of the polymerase gene in sequential samples from Patient B during ADV and LMV treatment.  
25

**Figure 8** is a representation showing comparison of the deduced amino acid sequence of the catalytic region of the polymerase gene in sequential samples from Patient B during ADV and LMV therapy.  
30



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**Figure 17** is a representation showing comparison of the deduced amino acid sequence of the catalytic region of the polymerase gene in sequential samples from Patient E during ADV therapy.

- 5 **Figure 18** is a representation showing comparison of the deduced amino acid sequence of the envelope gene in sequential samples from Patient E during ADV therapy.

**Figure 19** is a diagrammatic representation of a system used to carry out the instructions encoded by the storage medium.

10

**Figure 20** is a representation showing the nucleotide sequence of envelope/rt region of an HBV isolated from Patient F having ADV therapy.

- 15 **Figure 21** is a representation showing the deduced amino acid sequence of DNA polymerase encoded by the nucleotide sequence shown in Figure 20.

**Figure 22** is a representation showing the deduced amino acid sequence of HBsAg encoded by the nucleotide sequence shown in Figure 20.

- 20 **Figure 23** is a representation showing the nucleotide sequence of envelope/rt region of an HBV isolated from Patient G having ADV therapy.

**Figure 24** is a representation showing the deduced amino acid sequence of DNA polymerase encoded by the nucleotide sequence shown in Figure 23.

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**Figure 25** is a representation showing the deduced amino acid sequence of HBsAg encoded by the nucleotide sequence shown in Figure 23.

- 30 **Figure 26** is a representation showing the nucleotide sequence of envelope/rt region of an HBV isolated from Patient H having ADV therapy.

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## DETAILED DESCRIPTION OF THE INVENTION

The present invention is predicated in part on the identification and isolation of nucleoside or nucleotide analog-resistant variants of HBV following treatment of patients with either ADV or LMV or more particularly ADV and LMV, or optionally other nucleoside analogs or nucleotide analogs or other anti-HBV agents such as TFV or FTC. In particular, ADV or ADV and LMV treated patients gave rise to variants of HBV exhibiting decreased or reduced sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV. . Reference herein to "decreased" or "reduced" in relation to sensitivity to ADV and/or LMV and/or FTC and/or TFV includes and encompasses a complete or substantial resistance to the nucleoside or nucleotide analog or other anti-HBV agents as well as partial resistance and includes a replication rate or replication efficiency which is more than a wild-type in the presence of a nucleoside or nucleotide analog or other anti-HBV agents. In one aspect, this is conveniently measured by an increase in viral load during treatment, or alternatively, there is no substantial decrease in HBV DNA viral load from pre-treatment HBV DNA levels during treatment (i.e., non-response to treatment).

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Before describing the present invention in detail, it is to be understood that unless otherwise indicated, the subject invention is not limited to specific formulations of components, manufacturing methods, dosage regimens, or the like, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

25

It must be noted that, as used in the subject specification, the singular forms "a", "an" and "the" include plural aspects unless the context clearly dictates otherwise. Thus, for example, reference to "a nucleoside or nucleotide analog" includes a single analog, as well as two or more analogs; reference to "an HBV variant" includes reference to two or more HBV variants; and so forth.

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and/or the function of an enzyme such as HBV DNA polymerase. Furthermore, an "effective HBV-inhibiting amount" or "effective symptom-ameliorating amount" of an agent is a sufficient amount of the agent to directly or indirectly inhibit replication, infection, maintenance, assembly and/or the function of an enzyme such as HBV DNA polymerase. Undesirable effects, e.g. side effects, are sometimes manifested along with the desired therapeutic effect; hence, a practitioner balances the potential benefits against the potential risks in determining what is an appropriate "effective amount". The exact amount required will vary from subject to subject, depending on the species, age and general condition of the subject, mode of administration and the like. Thus, it may not be possible to specify an exact "effective amount". However, an appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

By "pharmaceutically acceptable" carrier, excipient or diluent is meant a pharmaceutical vehicle comprised of a material that is not biologically or otherwise undesirable, i.e. the material may be administered to a subject along with the selected active agent without causing any or a substantial adverse reaction. Carriers may include excipients and other additives such as diluents, detergents, coloring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

Similarly, a "pharmacologically acceptable" salt, ester, emide, prodrug or derivative of a compound as provided herein is a salt, ester, amide, prodrug or derivative that this not biologically or otherwise undesirable.

The terms "treating" and "treatment" as used herein refer to reduction in severity and/or frequency of symptoms, elimination of symptoms and/or underlying cause, prevention of the occurrence of symptoms and/or their underlying cause, and improvement or remediation of damage in relation to HBV infection. Thus, for example, "treating" a patient involves prevention of HBV infection as well as treatment of a clinically HBV symptomatic individual by inhibiting HBV replication, infection, maintenance, assembly and/or the function of an enzyme such as HBV DNA polymerase. Thus, for example, the

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polymerase resulting in at least one amino acid addition, substitution and/or deletion to said DNA polymerase and wherein said variant exhibits decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, 5 TFV and FTC and LMV, or ADV and LMV and FTC, ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combination thereof.

HBV is a member of the Hepdnaviridae that includes also avian hepatitis viruses such as 10 Duck hepatitis B virus (DHBV) and hepatitis viruses from mammals such as woodchuck hepatitis virus (WHV). These viruses have similarity to HBV and may be used in *in vitro* and *in vivo* or animal model systems to investigate the equivalent HBV mutants and anti-viral sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or 15 ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV,

An "anti-HBV agent" includes a nucleoside or nucleotide analog, protein, chemical compound, RNA or DNA or RNAi or siRNA oligonucleotide.

20

Preferably, the decreased sensitivity is in respect of ADV. Alternatively, the decreased sensitivity is in respect of LMV. Alternatively, the decreased sensitivity is in respect of TFV. Alternatively, the decreased sensitivity is in respect of FTC. Alternatively, the decreased sensitivity is in respect of ADV and LMV. Alternatively, the decreased 25 sensitivity is in respect of ADV and TFV. Alternatively, the decreased sensitivity is in respect of LMV and TFV. Alternatively, the decreased sensitivity is in respect of ADV and FTC. Alternatively, the decreased sensitivity is in respect to FTC and TFV. Alternatively, the decreased sensitivity is in respect of FTC and LMV. Alternatively, the decreased sensitivity is in respect of ADV and LMV and TFV. Alternatively, the decreased sensitivity 30 is in respect to ADV and TFV and FTC. Alternatively, the decreased sensitivity is in respect to LMV and TFV and FTC. Alternatively, the decrease sensitivity is in respect of ADV and

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The present invention extends to a mutation and any domain of the HBV DNA polymerase and in particular regions F and G, and domains A through to E provided said mutation leads to decreased sensitivity to ADV and/ or LMV and/or TFV or combinations thereof. Regions F and G of the HBV DNA polymerase is defined by the amino acid sequence set forth in Formula I below [SEQ ID NO:1]:

### FORMULA I

L, X<sub>1</sub>, X<sub>2</sub>, D, W, G, P, C, X<sub>3</sub>, X<sub>4</sub>, H, G, X<sub>5</sub>, H, X<sub>6</sub>, I, R, B<sub>7</sub>, P, R, T, P, X<sub>8</sub>, R, V, X<sub>9</sub>, G, G,  
 10 V, F, L, V, D, K, N, P, H, N, T, X<sub>10</sub>, E, S, X<sub>11</sub>, L, X<sub>12</sub>, V, D, F, S, Q, F, S, R, G, X<sub>13</sub>, X<sub>14</sub>,  
 X<sub>15</sub>, V, S, W, P, K, F, A, V, P, N, L, X<sub>16</sub>, S, L, T, N, L, L, S\*

wherein:

- 15 X<sub>1</sub> is L, or R, or I
- X<sub>2</sub> is E, or D
- X<sub>3</sub> is T, or D, or A, or N, or Y
- X<sub>4</sub> is E, or D
- X<sub>5</sub> is E, or K, or Q
- 20 X<sub>6</sub> is H, or R, or N,
- X<sub>7</sub> is I, or T
- X<sub>8</sub> is A, or S
- X<sub>9</sub> is T or R
- X<sub>10</sub> is A, or T, or S
- 25 X<sub>11</sub> is R, or T
- X<sub>12</sub> is V, or G
- X<sub>13</sub> is S, or I, or T, or N, or V
- X<sub>14</sub> is T, or S, or H, or Y
- X<sub>15</sub> is R, or H, or K, or Q
- 30 X<sub>16</sub> is Q, or P;

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- X<sub>13</sub> is S or Y;  
X<sub>14</sub> is N or Q;  
X<sub>15</sub> is L or M;  
X<sub>16</sub> is K or Q;  
5 X<sub>17</sub> is Y or F;  
X<sub>18</sub> is R or W;  
X<sub>19</sub> is Y or L;  
X<sub>20</sub> is S or A;  
X<sub>21</sub> is I or V;  
10 X<sub>22</sub> is I or L;  
X<sub>23</sub> is V or G;  
X<sub>24</sub> is C or L;  
X<sub>25</sub> is A or S;  
X<sub>26</sub> is V or M;  
15 X<sub>27</sub> is V or T;  
X<sub>28</sub> is R or C;  
X<sub>29</sub> is F or P;  
X<sub>30</sub> is L or V;  
X<sub>31</sub> is A or V;  
20 X<sub>32</sub> is S or A;  
X<sub>33</sub> is V or L or M;  
X<sub>34</sub> is K or R;  
X<sub>35</sub> is S or T;  
X<sub>36</sub> is V or G;  
25 X<sub>37</sub> is Q or E;  
X<sub>38</sub> is L or S or R;  
X<sub>39</sub> is S or F;  
X<sub>40</sub> is F or Y;  
X<sub>41</sub> is T or A;  
30 X<sub>42</sub> is A or S;  
X<sub>43</sub> is V or I;

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## FORMULA I

L, X<sub>1</sub>, X<sub>2</sub>, D, W, G, P, C, X<sub>3</sub>, X<sub>4</sub>, H, G, X<sub>5</sub>, H, X<sub>6</sub>, I, R, X<sub>7</sub>, P, R, T, P, X<sub>8</sub>, R, V, X<sub>9</sub>, G, G,  
 V, F, L, V, D, K, N, P, H, N, T, X<sub>10</sub>, E, S, X<sub>11</sub>, L, X<sub>12</sub>, V, D, F, S, Q, F, S, R, G, X<sub>13</sub>, X<sub>14</sub>,  
 5 X<sub>15</sub>, V, S, W, P, K, F, A, V, P, N, L, X<sub>16</sub>, S, L, T, N, L, L, S\*

wherein:

- X<sub>1</sub> is L, or R, or I  
 10 X<sub>2</sub> is E, or D  
 X<sub>3</sub> is T, or D, or A, or N, or Y  
 X<sub>4</sub> is E, or D  
 X<sub>5</sub> is E, or K, or Q  
 X<sub>6</sub> is H, or R, or N,  
 15 X<sub>7</sub> is I, or T  
 X<sub>8</sub> is A, or S  
 X<sub>9</sub> is T or R  
 X<sub>10</sub> is A, or T, or S  
 X<sub>11</sub> is R, or T  
 20 X<sub>12</sub> is V, or G  
 X<sub>13</sub> is S, or L, or T, or N, or V  
 X<sub>14</sub> is T, or S, or H, or Y  
 X<sub>15</sub> is R, or H, or K, or Q  
 X<sub>16</sub> is Q, or P;

25

and

## FORMULA II

30 SX<sub>1</sub>LSWLSLDVSAAFYHX<sub>2</sub>PLHPAAMPHELLX<sub>3</sub>GSSGLX<sub>4</sub>RYV  
 ARLSSX<sub>5</sub>SX<sub>6</sub>X<sub>7</sub>XNX<sub>8</sub>QX<sub>9</sub>X<sub>10</sub>XXXXX<sub>11</sub>LHX<sub>12</sub>X<sub>13</sub>CSRX<sub>14</sub>LYVSLX<sub>15</sub>

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- X<sub>24</sub> is C or L;  
X<sub>25</sub> is A or S;  
X<sub>26</sub> is V or M;  
X<sub>27</sub> is V or T;  
5 X<sub>28</sub> is R or C;  
X<sub>29</sub> is F or P;  
X<sub>30</sub> is L or V;  
X<sub>31</sub> is A or V;  
X<sub>32</sub> is S or A;  
10 X<sub>33</sub> is V or L or M;  
X<sub>34</sub> is K or R;  
X<sub>35</sub> is S or T;  
X<sub>36</sub> is V or G;  
X<sub>37</sub> is Q or E;  
15 X<sub>38</sub> is L or S or R;  
X<sub>39</sub> is S or F;  
X<sub>40</sub> is F or Y;  
X<sub>41</sub> is T or A;  
X<sub>42</sub> is A or S;  
20 X<sub>43</sub> is V or I;  
X<sub>44</sub> is T or C;  
X<sub>45</sub> is N or S;  
X<sub>46</sub> is F or V;  
X<sub>47</sub> is S or D;  
25 X<sub>48</sub> is L or V;  
X<sub>49</sub> is N or Q;  
X<sub>50</sub> is V or I; and  
M\* is amino acid 204;

- 30 and wherein S\* in Formula I is designated as amino acid 74 and the first S in Formula II is designated as amino acid 75;



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The term "combination therapy" means that both combinations of ADV, LMV, FTC and/or TFV are co-administered in the same composition or simultaneously in separate compositions. The term "sequential therapy" means that the two agents are administered within seconds, minutes, hours, days or weeks of each other and in either order. Sequential therapy also encompasses completing a therapeutic course with one or other of ADV, LMV, FTC or TFV and then completing a second or third or subsequent therapeutic courses with the other of ADV, LMV, FTC or TFV.

Accordingly, another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to ADV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to LMV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Yet another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to FTC therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

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of a subject to LMV and TFV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to ADV and FTC therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Yet another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to TFV and FTC therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Still another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to FTC and LMV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Even yet another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile

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wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to ADV, FTC and TFV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

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Still yet another aspect of the present invention contemplates an HBV variant comprising a surface antigen having an amino acid sequence with a single or multiple amino acid substitution, addition and/or deletion or truncation compared to the pretreatment HBV and wherein the surface antigen of the variant HBV exhibits an altered immunological profile compared to the pretreatment HBV where the said variant HBV is selected for by exposure of a subject to ADV, LMV, FTC and TFV therapy or therapy by one or more other nucleoside or nucleotide analogs or other anti-HBV agents.

Preferably, the variants are in isolated form such that they have undergone at least one purification step away from naturally occurring body fluid. Alternatively, the variants may be maintained in isolated body fluid or may be in DNA form. The present invention also contemplates infectious molecular clones comprising the genome or parts thereof from a variant HBV. Furthermore, the present invention provides isolated components from the variant HBVs such as but not limited to an isolated HBsAg. Accordingly, the present invention provides an isolated HBsAg or a recombinant form thereof or derivative or chemical equivalent thereof, said HBsAg being from a variant HBV selected by exposure of a subject to one or more of ADV, LMV, FTC and/or TFV or optionally one or more nucleoside or nucleotide analogs or other anti-HBV agents.

More particularly, yet another aspect of the present invention is directed to an isolated variant HBsAg or a recombinant or derivative form thereof or a chemical equivalent thereof wherein said HBsAg or its recombinant or derivative form or its chemical equivalent exhibits an altered immunological profile compared to an HBsAg from a reference HBV, said HBsAg being from a variant HBV selected by exposure of a subject to one or more of ADV, LMV, FTC and/or TFV or optionally one or more nucleoside or nucleotide analogs or other anti-HBV agents.

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rtN238N/H; in a further embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37; in yet another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63; in still another embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtL91; in even yet another embodiment, rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in still yet another  
 5 embodiment, rtM204 and rtY203; in another embodiment, rt235, rt236, rt237, rt238 and rt239; in a further embodiment, rt247, rt248, rt249, rt250 and rt251; in yet another embodiment,

K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 10 P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
 P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 15 F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
 A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
 V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
 D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
 V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
 20 S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
 A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
 Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
 H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
 25 P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
 L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
 30 Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
 F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;

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numbering system is different to that in Australian Patent No. 734831 where the methionine residue in the YMDD motif within the polymerase gene is designated codon 550. In this regard, rtL180M and rtM204V correspond to L526M and M550V, respectively, in Australian Patent No. 734831. Corresponding mutations may also occur in  
5 envelope genes such as in one or more of PreS1, PreS2 and S. The mutations in S gene encoding HBsAg at sT118R, sP120T, sS143S/T, sD144A or sI195M also result in mutation in the in the polymerase gene rtY126C, rtT128N, rtF151S/F or rtM204V respectively.

10 Another potential mode of action of ADV and other acyclic nucleoside phosphonates is that of immune stimulation (Calio *et al.*, *Antiviral Res.* 23: 77-89, 1994). A number of mutations resulted in changes in the envelope gene detected in HBV variants which may be associated with immune escape. These changes include sT118R, sP120T, sS126T, sM133T, sM133L/M, sF134V, sS143S/T, sD144A, sG145A and/or sW172STOP.

15 HBV encoding the mutation at codon sG145R is a well characterized vaccine escape mutant, although the envelope protein from HBV encoding the mutation at sG145A does not have the same antigen/antibody binding characteristics as the sG145R. This mutation was detected in HBV isolated from patient C in conjunction with mutations at codons 143  
20 and 144.

The identification of the variants of the present invention permits the generation of a range of assays to detect such variants. The detection of such variants may be important in identifying resistant variants to determine the appropriate form of chemotherapy and/or to  
25 monitor vaccination protocols, or develop new or modified vaccine preparations.

Still another aspect of the present invention contemplates a method for determining the potential for an HBV to exhibit reduced sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV,  
30 or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other

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another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37); in another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63); in a further embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91); in yet another embodiment, rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in still another embodiment, rtM204 and  
5 rtY203; in even yet another embodiment, rt235, rt236, rt237, rt238 and rt239 and in even still another embodiment, rt247, rt248, rt249, rt250 and rt251 and in another embodiment, K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M//deletionF;  
10 H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
15 A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
20 A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
25 F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
30 F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;

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mutation selected from, in one embodiment, rtS21A, rtL122F, rtN124H, rtH126R, rtT28N, rtP130Q, rtD131N and rtY135C; in another embodiment, rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M; in a further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, 5 rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A; in still another embodiment, rtH90D and rtL/F108L; in even yet another embodiment, sP120T, sM125T and sT127A; in still yet another embodiment, sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C; in another embodiment, sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop; 10 in a further embodiment, sN40S, sC69STOP, sM75I, sL88P, sT118A, sW182Stop, sW196L, sY206H and sY225F; in yet another embodiment, sI81M and sP214Q; in still another embodiment, sF83S, sL173F and sW199L; in yet another embodiment, sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C; in still another embodiment, sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop, 15 sS207R; in even still another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37); in another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63); in a further embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91); in yet another embodiment, rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in still another embodiment, rtM204 and rtY203; in even yet another embodiment, rt235, rt236, rt237, rt238 and 20 rt239 and in even still another embodiment, rt247, rt248, rt249, rt250 and rt251; and in another embodiment,

K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 25 H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
 P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
 30 A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
 V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;

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M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;

G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and

V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion or combinations thereof or an equivalent one or more other mutation is indicative of a variant which exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combination thereof.

10

A further aspect of the present invention produces a method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside or nucleotide analog or other anti-HBV agents, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding the DNA polymerase and/or a corresponding region of the S gene, wherein the presence of a mutation selected from, in one embodiment, rtS21A, rtL122F, rtN124H, rtH126R, rtT28N, rtP130Q, rtD131N and rtY135C; in another embodiment, rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M; in a further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A; in still another embodiment, rtH90D and rtL/F108L; in even yet another embodiment, sP120T, sM125T and sT127A; in still yet another embodiment, sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C; in another embodiment, sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop; in a further embodiment, sN40S, sC69STOP, sM75I, sL88P, sT118A, sW182Stop, sW196L, sY206H and sY225F; in yet another embodiment, sI81M and sP214Q; in still another embodiment, sF83S, sL173F and sW199L; in yet another embodiment, sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C; in still another embodiment, sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop, sS207R; in even still another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37); in another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63); in a further embodiment,

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M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
 L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
 5 P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
 N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
 S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
 10 Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
 K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
 L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
 N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
 H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
 15 F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
 M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
 G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
 V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion or combinations thereof or an  
 equivalent one or more other mutation is indicative of a variant which exhibits a decreased  
 20 sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and  
 TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV  
 and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC  
 and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-  
 HBV agents or combination thereof.

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The detection of HBV or its components in cells, cell lysates, cultured supernatant fluid  
 and bodily fluid may be by any convenient means including any nucleic acid-based  
 detection means, for example, by nucleic acid hybridization techniques or *via* one or more  
 polymerase chain reactions (PCRs). The term "bodily fluid" includes any fluid derived  
 30 from the blood, lymph, tissue or organ systems including serum, whole blood, biopsy and  
 biopsy fluid, organ explants and organ suspension such as liver suspensions. The invention

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Another aspect of the present invention contemplates a method for detecting an agent which exhibits inhibitory activity to an HBV by:

generating a genetic construct comprising a replication competent-effective  
5 amount of the genome from the HBV contained in a plasmid vector and then transfecting  
said cells with said construct;

contacting the cells, before, during and/or after transfection, with the agent to  
be tested;  
10

culturing the cells for a time and under conditions sufficient for the HBV to  
replicate, express genetic sequences and/or assemble and/or release virus or virus-like  
particles if resistant to said agents; and

15 then subjecting the cells, cell lysates or culture supernatant fluid to viral- or  
viral-component-detection means to determine whether or not the virus has replicated,  
expressed genetic material and/or assembled and/or been released in the presence of the  
agent.

20 In a preferred embodiment, the plasmid vector may include genes encoding part or all of  
other viral vectors such as baculovirus or adenovirus (Ren and Nassal, 2001, *supra*) and the  
method comprises:

generating a genetic construct comprising a replication competent-effective  
25 amount of the genome from the HBV contained in or fused to an amount of a baculovirus  
genome or adenovirus genome effective to infect cells and then infecting said cells with  
said construct;

contacting the cells, before, during and/or after infection, with the agent to be  
30 tested;

further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A; in still another embodiment rtH90D and rtL/F108L; in even yet  
5 another embodiment, rtL157L/M, rtA181V and rtV207I; in even still another embodiment, rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K; in another embodiment, rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H; in a further embodiment, sP120T, sM125T and sT127A; in yet another embodiment, sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C; in still  
10 another embodiment, sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop; in even yet another embodiment, sN40S, sC69Stop, sM75I, sL88P, sT118A, sW182STOP, sW196L, sY206H and sY225F; in even still another embodiment, s181M and sP214Q; in another embodiment, sF83S, sL173F and sW199L; in a further embodiment, sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C; in yet another  
15 embodiment, sC69Stop/C, sC76Y sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R; in still another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37; in even yet another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63; in even still another embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91; in another embodiment, rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in a  
20 further embodiment, rtM204 and rtY203; in yet another embodiment, rt235, rt236, rt237, rt238 and rt239 in still another embodiment, rt247, rt248, rt249, rt250 and rt251; and in even yet another embodiment, K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion; N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion; P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
25 H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion; T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion; P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion; K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion; F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
30 A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion; V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;

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M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
 G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
 V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion.

- 5 Accordingly, another aspect of the present invention contemplates a method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside or nucleotide analog or other potential anti-HBV agent, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence of the envelope genes or DNA polymerase gene selected from, in one
- 10 embodiment, rtS21A, rtL122F, rtN124H, rtH126R, rtT28N, rtP130Q, rtD131N and rtY135C; in another embodiment, rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M; in a further embodiment, rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D; in yet another embodiment, rtS78T, rtV84M,
- 15 rtY126C, rtV191I, rtM204I and rtV214A; in still another embodiment rtH90D and rtL/F108L; in even yet another embodiment, rtL157L/M, rtA181V and rtV207I; in even still another embodiment, rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K; in another embodiment, rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H; in a further embodiment, sP120T, sM125T
- 20 and sT127A; in yet another embodiment, sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C; in still another embodiment, sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop; in even yet another embodiment, sN40S, sC69Stop, sM75I, sL88P, sT118A, sW182STOP, sW196L, sY206H and sY225F; in even still another embodiment, s181M and sP214Q; in another embodiment, sF83S, sL173F and sW199L; in a further
- 25 embodiment, sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C; in yet another embodiment, sC69Stop/C, sC76Y sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R; in still another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37; in even yet another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63; in even still another embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91; in
- 30 another embodiment, rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in a further embodiment, rtM204 and rtY203; in yet another embodiment, rt235, rt236,

- T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
5 A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I;  
10 N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M;  
M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K;  
G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/QE; and  
15 V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion or combinations thereof or an  
equivalent one or more other mutation is indicative of a variant wherein said variant  
exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV  
and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and  
LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and  
20 FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or  
nucleotide analogs or other anti-HBV agents or combination thereof.

The detection of amino acid variants of DNA polymerase is conveniently accomplished by  
reference to the amino acid sequence shown in Formulae I and II. The polymorphisms  
25 shown represent the variations shown in various databases for active pathogenic HBV  
strains. Where an HBV variant comprises an amino acid different to what is represented,  
then such an isolate is considered a putative HBV variant having an altered DNA  
polymerase activity.

30 The present invention further contemplates agents which inhibit ADV, LMV, TFV, or  
FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV,

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culturing said cells for a time and under conditions sufficient for the HBV to replicate, express genetic sequences and/or assemble and/or release virus or virus-like particles if resistant to said agent; and

5           subjecting the cells, cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed genetic material and/or assembled and/or been released in the presence of said agent.

Still another aspect of the present invention provides a method for detecting an agent  
10   which exhibits inhibitory activity to an HBV which exhibits resistance or decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-  
15   HBV agents or combination thereof, , said method comprising:

          generating a genetic construct comprising a replication competent-effective amount of the genome from said HBV contained in or fused to an amount of a baculovirus genome effective to infect cells and then infecting said cells with said construct;

20           contacting said cells, before, during and/or after infection, with the agent to be tested;

          culturing said cells for a time and under conditions sufficient for the HBV to  
25   replicate, express genetic sequences and/or assemble and/or release virus or virus-like particles if resistant to said agent; and

          subjecting the cells, cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed  
30   genetic material and/or assembled and/or been released in the presence of said agent.

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Several models of the HBV polymerase have been prepared due to the similarity with reverse transcriptase from HIV (Das *et al.*, *J. Virol.* 75(10): 4771-4779, 2001; Bartholomeusz *et al.*, *Intervirology* 40(5-6): 337-342 1997; Allen *et al.*, *Hepatology* 27(6): 1670-1677, 1998). The models of the HBV polymerase can be used for the rational drug design of new agents effective against HBV encoding the resistant mutations as well as wild type virus. The rational drug that is designed may be based on a modification of an existing antiviral agent such as the agent used in the selection of the HBV encoding the mutations associated with resistance. Viruses or clones expressing HBV genomic material encoding the mutations may also be used to screen for new antiviral agents.

In an alternative embodiment, the present invention also contemplates a method for detecting an agent which exhibits inhibitory activity to an HBV polymerase in an *in vitro* polymerase assay. The HBV polymerase activity can be examined using established assays (Gaillard *et al.*, *Antimicrob Agents Chemother.* 46(4): 1005-1013, 2002; Xiong *et al.*, *Hepatology* 28(6): 1669-1673, 1998).

As indicated above, microarray technology is also a useful means of identifying agents which are capable of interacting with defined HBV internal or external components. For example, arrays of HBV DNA polymerase or peptide fragments thereof carrying different amino acid variants may be used to screen for agents which are capable of binding or otherwise interacting with these molecules. This is a convenient way of determining the differential binding patterns of agents between HBV variants. Arrays of antibodies may also be used to screen for altered HBsAg molecules. Microarrays are also useful in proteomic analysis to identify molecules such as antibodies, interferons or cytokines which have an ability to interact with an HBV component. Microarrays of DNA and RNA molecules may also be employed to identify sense and antisense molecules for genetic regions on the HBV genome or transcripts thereof.

The above methods are particularly useful in identifying an inhibitor of an HBV resistant to or exhibiting reduced sensitivity to ADV, LMV, TFC, or FTC, or ADV and LMV, ADV

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Pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi.

5 The carrier can be a solvent or dilution medium comprising, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof and vegetable oils. The proper fluidity can be maintained, for example, by the use of surfactants. The prevention of the action of microorganisms can be brought about by various anti-bacterial and anti-fungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminium monostearate and gelatin.

15

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with the active ingredient and optionally other active ingredients as required, followed by filtered sterilization or other appropriate means of sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, suitable methods of preparation include vacuum drying and the freeze-drying technique which yield a powder of active ingredient plus any additionally desired ingredient.

20

When the active ingredient is suitably protected, it may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets. For oral therapeutic administration, the active ingredient may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight

25

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Yet another aspect of the present invention provides a composition comprising a variant HBV resistant to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or an HBV surface antigen from said variant HBV or a recombinant or derivative form thereof or its chemical equivalent and one or more pharmaceutically acceptable carriers and/or diluents. Such a composition may be regarded as a therapeutic composition and is useful in generating an immune response including a humoral response.

10 Generally, the HBV variants are "defective" and in themselves are unable to cause a sustained infection in a subject.

As indicated above, antibodies may be generated to the mutant HBV agents and used for passive or direct vaccination against infection by these viruses. The antibodies may be generated in humans or non-human animals. In the case of the latter, the non-human antibodies may need to be deimmunized or more specifically humanized prior to use. Deimmunized may include, for example, grafting complementarity determining regions (CDRs) from the variable region of a murine or non-human animal anti-HBV antibody onto a human consensus fragment antibody binding (Fab) polypeptide. Alternatively,

15 amino acids defining epitopes in the variable region of the antibody may be mutated so that the epitopes are no longer recognized by the human MHC II complex.

Insofar as ribozyme, antisense or co-suppression (RNAi) or siRNA or complexes thereof repression is concerned, this is conveniently aimed at post-transcription gene silencing.

25 DNA or RNA may be administered or a complex comprising RNAi or a chemical analog thereof specific for HBV mRNA may be employed.

All such molecules may be incorporated into pharmaceutical compositions.

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sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop; in even yet another embodiment, sN40S, sC69Stop, sM75I, sL88P, sT118A, sW182STOP, sW196L, sY206H and sY225F; in even still another embodiment, sI81M and sP214Q; in another embodiment, sF83S, sL173F and sW199L; in a further embodiment, sI126T, sK160R, 5 sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C; in yet another embodiment, sC69Stop/C, sC76Y sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R; in still another embodiment, rtK32, rtN33, rtP34, rtH35 and rtT37; in even yet another embodiment, rtP59, rtK60, rtF61, rtA62 and rtV63; in even still another embodiment, rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91; in another embodiment, rtP177, 10 rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184; in a further embodiment, rtM204 and rtY203; in yet another embodiment, rt235, rt236, rt237, rt238 and rt239 in still another embodiment, rt247, rt248, rt249, rt250 and rt251; and in even yet another embodiment,

K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;

15 N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;

P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;

H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;

T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;

P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;

20 K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;

F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;

A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;

V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;

D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;

25 V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;

S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;

A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;

Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;

H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;

30 I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;

P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;

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cause infection. Such a defective, nucleoside analog-resistant virus may then be used as a therapeutic vaccine against virulent viruses having the same mutation in its polymerase.

The subject invention extends to kits for assays for variant HBV resistant to ADV, LMV, 5 TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV.. Such kits may, for example, contain the reagents from PCR or other nucleic acid hybridization technology or reagents for immunologically based detection techniques. A particularly 10 useful assay includes the reagents and components required for immobilized oligonucleotide- or oligopeptide-mediated detection systems.

Still another aspect of the present invention contemplates a method for determining the potential for an HBV to exhibit reduced sensitivity to ADV, LMV, TFV, or FTC, or ADV 15 and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combination thereof, said method comprising isolating DNA or corresponding mRNA from said HBV and screening 20 for a mutation in the nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in any one or more of domains F and G, and domains A through to E or a region proximal thereto of said DNA polymerase and associated with resistance or decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and 25 LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, wherein the presence of such a mutation is an indication of the likelihood of resistance to said ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC 30 and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV.

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- (3) a computer readable medium that stores the codes.

In a related aspect, the invention extends to a computer for assessing the likely usefulness of a viral variant or biological sample comprising same in a subject, wherein said computer  
5 comprises:

- (1) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said machine-readable data comprise I<sub>vs</sub> for at least two features associated with said viral variant or biological sample; wherein said features are selected from:-  
10
- (a) the ability to exhibit resistance for reduced sensitivity to a particular compound or immunological agent;
  - (b) an altered DNA polymerase from wild-type HBV;
  - 15 (c) an altered surface antigen from wild-type HBV;
  - (d) morbidity or recovery potential of a patient; or
  - (e) altered replication capacity (increased or decreased);
- (2) a working memory for storing instructions for processing said machine-readable data;  
20
- (3) a central-processing unit coupled to said working memory and to said machine-readable data storage medium, for processing said machine readable data to provide a sum of said I<sub>vs</sub> corresponding to a P<sub>v</sub> for said compound(s); and  
25
- (4) an output hardware coupled to said central processing unit, for receiving said P<sub>v</sub>.

Any general or special purpose computer system is contemplated by the present invention and includes a processor in electrical communication with both a memory and at least one  
30 input/output device, such as a terminal. Figure 19 shows a generally suitable computer system. Such a system may include, but is not limited, to personal computers, workstations

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rt237, rt238 and rt239 in still another embodiment, rt247, rt248, rt249, rt250 and rt251; and in even yet another embodiment,

- K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
5 P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
10 F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
15 S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
20 P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
25 Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
30 L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;

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## EXAMPLE 1

### *Overlapping genome of HBV*

The overlapping genome of HBV is represented in Figure 1. The gene encoding DNA  
5 polymerase (P), overlaps the viral envelope genes, Pre-S1 and Pre-S2, and partially  
overlaps the X and core (C) genes. The HBV envelope comprises small, middle and large  
proteins HBV surface antigens. The large protein component is referred to as the HBV  
surface antigen (HBsAg) and is encoded by the S gene sequence. The Pre-S1 and Pre-S2  
gene sequences encode the other envelope components.

10

## EXAMPLE 2

### *Patients and Treatment*

Patient A, a 48 year old Lebanese woman was initially referred for evaluation of  
15 thrombocytopenia and hepatosplenomegaly. At this time the patient had abnormal LFT's  
(ALT 67 U/L, normal <55) and the HBV DNA was 61 pg/ml (231 days prior to the start of  
treatment). The patient was HBsAg and HBeAg positive. The ALT's fluctuated between  
50-70 IU/L from (-231 to -35 days pretreatment). ADV was commenced on Day 0 in a  
clinical trial on 30 mg/day. HBV DNA levels were reduced with ADV treatment. The  
20 ADV treatment was reduced to 10 mg /day (144 days post-treatment). There was a  
problem with the randomization treatment protocol. The patient was on antiviral treatment  
for 1 month only during the second year of the treatment period. The study was completed  
on Day 679 post ADV treatment. The patient was not on ADV treatment until the open  
label ADV was recommenced on Day 875 from the start of the initial ADV treatment. This  
25 second period of ADV treatment was given for 108 days (day 983 post initial ADV  
treatment). The HBV DNA levels remained at 7-10 pg/ml ( $1.96 \times 10^5$  to  $2.8 \times 10^5$   
copies/ml). At Day 983, ADV treatment was stopped and the patient was treated with  
LMV.

30 Patient B is a male liver transplant patient. The patient has been on both sequential and  
combination antiviral therapy including HBIG, FCV+HBIG, LMV+HBIG, LMV,

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## EXAMPLE 4

### *Sequencing of HBV DNA*

HBV DNA was extracted from 100 µl of serum as described previously by Aye *et al.*, *J. Hepatol.* 26: 1148-1153, 1997. Oligonucleotides were synthesized by Geneworks, Adelaide, Australia. Amplification of the HBV polymerase gene has been described by Aye *et al.*, 1997, *supra*.

The specific amplified products were purified using PCR purification columns from MO BIO Laboratories Inc (La Jolla, CA) and directly sequenced using Big Dye terminator Cycle sequencing Ready Reaction Kit (Perkin Elmer, Cetus Norwalk, CT). The PCR primers were used as sequencing primers, OS1 5'- GCC TCA TTT TGT GGG TCA CCA TA-3' (nt 1408-1430) [SEQ ID NO:3], TTA3 5'-AAA TTC GCA GTC CCC AAA-3'(nt2128-2145) [SEQ ID NO:4], JM 5'-TTG GGG TGG AGC CCT CAG GCT - 3'(nt1676-1696) [SEQ ID NO:5], TTA4 5'-GAA AAT TGG TAA CAG CGG -3' (nt 2615-2632) [SEQ ID NO:6], OS2 5' TCT CTG ACA TAC TTT CCA AT 3' (nt 2798-2817) [SEQ ID NO:7], to sequence the internal regions of the PCR products.

## EXAMPLE 5

### *Analysis of HBV DNA*

Patient A: During ADV treatment, unique HBV mutations were detected by sequencing (Tables 4 and 5) This includes the unique mutation at rtY135C in addition to the mutation at rtT128N that was present prior to ADV treatment. A number of other unique changes were also detected in the polymerase and in the overlapping envelope gene (Table 5, Figures 4, 5 and 6). The unique change in the HBsAg include sP120T. These unique changes were compared to reference sequences from each of the seven genotypes A-G as well as a consensus sequence from pretreatment samples to determine unique changes.

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**EXAMPLE 7*****HBV rt mutants***

The HBV polymerase has similarities to other polymerases including HIV. Thus, mutations associated with resistance to antiviral agents may occur within the polymerase in functionally important regions such as the nucleotide triphosphate binding pocket that may also include the interaction between the DNA primer and template strand, magnesium ions and nucleoside triphosphates or nucleoside/ nucleotide analogs (and there vaious phosphroylated forms). Codons which are proposed to be mutated during anti-viral selection pressure are rtK32, rt N33, rtP34, rtH35 and rtT37 (that are upstream from the F domain); rt P59, rtK60, rtF61, rtA62 and rtV63 (between the F and A domains), rtD83, rtV84, rtS85, rtA86, rt Y89, rt H90 and rtI/L91 (within the A domain and the region immediately prior to and after), rtP177, rtF178, rt L179, rtL180, rtA181, rtQ182, rtF183 and rtT184 (B domain); rtM204 and rtY203(C Domain), rtL235, rtN236, rtP/T237, rtN/H/A/S/Q238 and rtK239 (D Domain), rLt247, rtN/H248, rtF249, rtM250 and rtG251 (E Domain). The codons are defined in Table 12 and examples of various mutants are given in Tables 13 and 14.

**EXAMPLE 8**

20

***Patient F***

The HBV mutations during ADV treatment of Patient F are listed in Table 15 and Figures 20, 21 and 22. The unique changes in the HBV DNA polymerase includes rtL157L/M, rtA181V, rtV207I, and rtN236T. The unique changes in the surface includes sF83S, sL173F and sW199L.



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Gaithersburg, MD) in humidified incubator at 28°C with CO<sub>2</sub>. HepG2 cells were maintained in minimal essential medium supplemented with 10% v/v heat-inactivated fetal bovine serum (MEM-FBS). HepG2 cells were grown in humidified 37°C incubators at 5% v/v CO<sub>2</sub>.

5

### EXAMPLE 13

#### *Preparation of HBV/baculovirus transfer vector with specific point mutations*

The recombinant HBV/baculovirus system used for antiviral testing has been previously described (Delaney *et al.*, *Antimicrob Agents Chemother* 45(6): 1705-1013, 2001). In brief, the recombinant transfer vector was created by excising a fragment containing the 1.3x HBV genome construct and cloning it into the multiple cloning region of a baculovirus vector pBlueBac4.5 (Invitrogen, Carlsbad, CA). Point mutations were created by site directed mutagenesis using the commercial kits according to the manufacturer's specifications (QuikChange, Stratagene). HBV/ baculovirus recombinant clones encoding the reverse transcriptase mutations rtA181T/N236T/N238D and rtN236T/N236D in combination with the precore mutation at G1896A (pcW28 stop) or wild-type with respect to codon pcW28, were prepared by site-directed mutagenesis. The nucleotide sequence of the plasmid and the point mutations generated by site directed mutagenesis were confirmed by sequencing using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit according to the manufacturer's specifications (Perkin Elmer, Cetus Norwalk, CT).

15  
20

### EXAMPLE 14

#### *Generation of recombinant baculoviruses containing the 1.3 HBV construct*

25

Purified recombinant transfer vector and linear AcMNPV baculovirus DNA were co-transfected into Sf21 cells using the BacNBlue transfection kit from Invitrogen (Carlsbad, CA); recombinant viruses were isolated by plaque assay according to the manufacturer's instructions. A series of recombinant viruses were amplified from isolated plaques by infecting 100-mm dishes of Sf21 cells. Viral DNA was extracted from amplified viruses

30

## EXAMPLE 16

### *Infection of HepG2 cells with recombinant HBV expressing baculovirus*

HepG2 cells were seeded at approximately 20-40% confluency and then were grown for  
 5 16-24 hours before infection. On the day of infection, triplicate plates of cells were  
 trypsinized, and viable cell number was determined with a hemocytometer using Trypan  
 blue exclusion. Average cell counts were calculated and used to determine the volume of  
 high-titer viral stock necessary to infect cells at the indicated moi. HepG2 cells were  
 washed one time with serum-free MEM to remove traces of serum. Baculovirus was  
 10 diluted into MEM without serum to achieve the appropriate moi using volumes of 1.0, 0.5,  
 and 0.25 ml to infect 100-mm, 60 mm, and 35-mm dishes, respectively. Baculovirus was  
 adsorbed to HepG2 cells for one hour at 37°C with gentle rocking every 15 minutes to  
 ensure that the inoculum was evenly distributed. The inoculum was then aspirated and  
 HepG2 cells were washed two times with phosphate-buffered saline and refed MEM-FBS  
 15 with or without various concentrations of agents.

## EXAMPLE 17

### *Detection of intracellular replicative intermediates*

20 HBV core particles were isolated from the-cytoplasmic fraction of HepG2 cells lysed in  
 0.5% w/v NP-40. Cytoplasmic extracts were adjusted to 10 mmol/l McC12 and  
 unprotected DNA was removed by an incubation to 500 g/ml Proteinase K for 1.5 hours at  
 37°C. HBV DNA in the samples were then extracted using commercial DNA extraction  
 kits such as Qiagen (DNA extraction) or in-house methods using sequential phenol and  
 25 chloroform extractions, and the nucleic acids were recovered by ethanol precipitation.  
 Nucleic acids were resuspended in 50 µl /l TE (10 mmol/l Tris, 1 mmol/l  
 ethylenediaminetetraacetic acid), normalized by OD260, and digested with 100 g/ml  
 RNase (Boehringer Mannheim, Indianapolis, IN) for one hour at 37°C before analysis by  
 real-time PCR or electrophoresis and Southern blotting. After southern blot analysis a  
 30 BioRad GS-670 imaging densitometer and the Molecular Analyst software (BioRad,  
 Hercules California) was used to analyze suitable exposures of Southern blots.

Densitometry data was fitted to logistic dose response curves using the TableCurve 2D software package from Jandel Scientific. Logistic dose response equations were used to calculate IC<sub>50</sub> and IC<sub>90</sub> values and co-efficients of variation.

5

## EXAMPLE 18

### *Real-time PCR*

For the real-time PCR based assay for HBV, HBV DNA was extracted from 200 µl of serum using the QIAamp DNA Mini Kit according to the manufacturer's instructions  
10 (QIAGEN GmbH, Hildens, Germany). Primers and a molecular beacon were designed for conserved nucleic acid sequences within the precore domain of the HBV genome to amplify and detect a 216-nucleotide product. Amplification was performed in a 50-µl reaction mixture containing 1.0 Taqman buffer A (Applied Biosystems, Foster City, CA), 3.0 mM MgCl<sub>2</sub>, 0.4 pmol of each primer per µL, forward primer, PC1 (5'-  
15 GGGAGGAGATTAGGTAA-3' [SEQ ID NO:12]) and reverse primer, PC2 (5'-GGCAAAAACGAGAGTAACTC-3' [SEQ ID NO:13]), 0.4 pmol of the HBV-specific molecular beacon per µL, (5'-FAM-CGCGTCCTACTGTTCAAGCCTCCAAGCTGT  
GACGCG-DABCYL-3' [SEQ ID NO:14]; where FAM represents fluorophore 6-carboxyfluorescein and DABCYL, 4-dimethylaminophenylazobenzoic acid, a quenching  
20 chromophore) and 1.25U of AmpliTaq Gold DNA polymerase (Perkin-Elmer). PCR was performed using the ABI PRISM 7700 spectrofluorometric thermocycler (Applied Biosystems). The PCR program consisted of an initial cycle (95°C for 10 minutes) followed by 45 amplification cycles (94°C for 15 secs, 50°C for 30 secs, 72°C for 30 secs). The instrument detected and recorded the fluorescence spectrum of each reaction tube  
25 during the annealing phase.

An external standard was constructed by ligation of a 1.3 kB wild-type HBV plasmid (genotype D) into the pBlueBac plasmid vector (Hershey Medical Center, Hershey, PA). Quantification of the DNA concentration of the plasmid was determined by  
30 spectrophotometry. Duplicates of serial 10-fold dilutions of the plasmid ranging from 10<sup>8</sup> copies/ml to 100 copies/ml were included in each run in order to generate a standard curve.

The copy number in each experimental reaction was determined by interpolation of the derived threshold cycle ( $C_T$ ).

## EXAMPLE 19

5

### *ADV treatments*

ADV was resuspended in sterile water, aliquoted, and frozen at  $-20^{\circ}\text{C}$  to avoid repeated freezing and thawing of the drug. Medium containing ADV was prepared daily as needed using fresh aliquots of 3TC. In experiments in which ADV treatment was initiated after  
10 viral infection, HepG2 cells were exposed to the indicated concentration of ADV immediately after infection with HBV baculovirus. In experiments utilizing pretreatment with ADV, cells were fed medium containing ADV 16 hours prior to HBV baculovirus infection, HBV baculovirus infection was also carried out in medium containing ADV, and cells were refed fresh medium containing ADV immediately after completion of the  
15 infection and washing procedures.

## EXAMPLE 20

### *Antiviral testing performed with wild-type and HBV/baculovirus encoding rtA181T/N236T/N238D and rtN236T/N236D*

20

The *in vitro* antiviral drug cross-resistance testing of the HBV mutants is shown in Table 18. The laboratory reference strain of HBV (genotype D subtype ayw) containing the introduced D domain mutations demonstrated increased  $\text{IC}_{50}$  values against ADV (Table 18). The rt N236T/N238D mutation was associated with a twenty-three fold increase in  
25  $\text{IC}_{50}$  against ADV. This was reduced to a five-fold increase when the rtA181T was also present and this triple HBV polymerase mutant was resistant to LMV.

**TABLE 4** Clinical, virological and HBV sequencing data summary for Patient A while on open label ADV.

5

Days post-ADV treatment	HBV DNA copies/ml (pg/ml)	ALT IU/L	Treatment protocol	Key polymerase mutations detected by sequencing <sup>1</sup>
-230	1.7 10 <sup>6</sup> (61)	67 U/L	pre-therapy	rtT/N128T/N rtQ/H/R215Q/stop
875			ADV recommenced	
904	1.55 x 10 <sup>6</sup>			
932	2.97 x 10 <sup>6</sup>			
959	1.76 x 10 <sup>6</sup>			
983	1.64 x 10 <sup>6</sup>	65	end ADV	rtT128N rtY135C

<sup>1</sup> Nomenclature according to Stuyver *et al.*, 2001, *supra*

**TABLE 5** Summary of HBV mutations in patient A treated with ADV

Sample name	Days post-ADV treatment	Genotype	Polymerase*	Surface
ILA1	-230	D	rtA/S21A/S <b>rtT/N128T/N**</b> <b>rtQ/H/R215Q/stop</b>	<b>sP120P/T</b> <b>sI208I/L</b>
ILA2	904	D	rtA/S21S rtF122L rtR126H rtT/N128T/N rtQ130P rtN131D rtQstop/215Q rtH248N	sP/T120P sT125M sI/208I/L
ILA3	932	D	rtA/S21S rtF122L rtR126H rtT/N128T/N rtQ130P rtN131D rtQstop/215Q rtH248N	sP/T120P sT125M sI/208I/L
ILA4	983	D	rtS21A rtL122F rtN124H rtH126R rtT128N rtP130Q rtD131N rtY135C	<b>sP120T</b> <b>sM125T</b> <b>sT127A</b>

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

5 \*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 6** Clinical, virological and HBV sequencing data summary for Patient B while on open label ADV.

Days post-ADV treatment	HBV DN copies/ml (pg/ml)	ALT IU/L	Treatment protocol	Key polymerase mutations detected by sequencing <sup>1</sup>
-867(S0)	183	298	pre-therapy	rtN/S/T/I/V53D rtV153G rtQ/E215S rtN248H
-8(S6)	955	427	pre-ADV on LMV	rtI/L80L rtY126Q rtL180M rtS202G rtI204V
76(S8)	not detected	150	on ADV (20 mg) and LMV	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G rtI204V
637(S12)	not detected	36	on ADV (5 mg) and LMV	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G rtI204V
872(S15)	not detected	67	on ADV (5 mg) and LMV	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G rtI204V rtI235I/M

5 <sup>1</sup> Nomenclature according to Stuyver *et al.*, 2001, *supra*

TABLE 7 Summary of HBV mutations in Patient B treated with ADV

Sample name	Days post-ADV treatment	Genotype	Polymerase*	Surface
S0	-867	D	rtN/S/T/I/V53D rtV153G rtQ/E215S rtN248H	sM/K/L133T sF134V sS207R sL21V/L
S6	-8	D	rtI/L80L rtY126Q rtL180M rtS202G rtI204V	sT118R sM133T sF134V sI195M sS207R
S8	76	D	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G rtI204V	sT118R sM133T sF134V sI195M sS207R
S12	637	D	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G I204V	sT118R sM133T sF134V sI195M sS207R
S15	872	D	rtN/S/T/I/V53D rtY126Q rtL180M rtS202G rtI204V rtI235I/M	sT118R sM133T sF134V sI195M sS207R sY225Y/C

5 \* Nomenclature according to Stuyver *et al.*, 2001, *supra*

\*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.



**TABLE 8** Clinical, virological and HBV sequencing data summary for Patient C while on open label ADV.

Days post-ADV treatment	HBV DNA copies/ml (pg/ml)	ALT IU/L	Treatment protocol	Key polymerase mutations detected by sequencing <sup>1</sup>
-26	2 x 10 <sup>7</sup>		pre-therapy	rtN53D rtS116P rtD/N/S134V rtN238D
0		240	ADV commenced clinical trial	
29		160		
630		407		
668			Open label ADV	
701	1.5 x 10 <sup>7</sup>	226		
730	3.7 x 10 <sup>6</sup>	361		rtN53D rtS116P rtF151S/T rtA181T rtN236T rtN238D
738		517		
739			end ADV, start LMV	

5 <sup>1</sup> Nomenclature according to Stuyver *et al.*, 2001, *supra*

TABLE 9 Summary of HBV mutations in Patient C treated with ADV

Sample name	Days post-ADV treatment	Genotype	Polymerase*	Surface
DRJ1299	-26	D	rtN53D** rtY54H rtS57P rtL91I rtS116P rtF122L rtY124H rtD/N/S134V rtK212R rtL217R rtS219A rtN238D	T126S S204G L209V S210R
DRJ1	730	D	rtN53D rtY54H rtS57P rtL91I rtS116P rtF122L rtY124H rtV134D rtY141Y/F rtL145M rtF151T/F rtA181T rtK212R rtL217R rtS219A rtN236T rtN238D	sS126T sM133L/M sS143S/T sD144A sG145A sW172Stop

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

5 \*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 10** Summary of HBV mutations in Patient D treated with ADV

Sample Name	Genotype	Polymerase*	Surface
02575908	D	rtS78T rtV84M rtY126C rtV191I rtM204I rtV214A	sN40S  sC69stop sM75I sL88P sT118A sW182STOP sW196L sY206H sY225F

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

5 \*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 11** Summary of HBV mutations in Patient E treated with ADV

Sample Name	Genotype	Polymerase*	Surface
8123/02	A	rtH90D rtL/F108L 6nt insertion/duplication after codon rt131(aaQ&N)	sI81M sY/S100Y 6nt insertion/ duplication after codon s122 (aaT & K) sP214Q

10

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

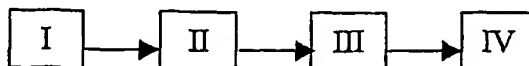
\*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 12** Codons where mutations occur following exposure to nucleoside or nucleotide analogs

Region/ Domain	Original amino acid in reverse transcriptase (rt) and codon position	Nucleotide				
prior to F	K32	AAG	AAA			
	N33	AAT				
	P34	CCT				
	H35	CAC				
	T37	ACC				
F TO A	P59	CCA				
	K60	AAA				
	F61	TTC				
	A62	GCA				
	V63	GTC				
A	D83	GAT				
	V84	GTG				
	S85	TCT				
	A86	GCG				
	Y89	TAT				
	H90	CAT				
	I/L91	ATT	CTT			
B	P177	CCG				
	F178	TTT				
	L179	CTC				
	L180	CTG				
	A181	TTG				
	Q182	CAG				
	F183	TTT				
	T184	ACT				
C	Y203	TAT				
	M204	ATG				
D	L235	TTG	TTA			
	N236	AAC	AAT			
	T237	ACT	ACC			
	P237	CCT	CCC			
	N238	AAT	AAC			
	H238	CAC				
	A238	GCT				
	S238	TCT				
	Q238	CAG				

Region/ Domain	Original amino acid in reverse transcriptase (rt) and codon position	Nucleotide				
	K239	AAA	AAG			
E	L247	CTT	TTA	CTA	CTC	CTG
	N248	AAC	AAT			
	H248	CAT	CAC			
	F249	TTC	TTT			
	M250	ATG				
	G251	GGT	GGA	GGC	GGG	
	V251	GTC				

**TABLE 13** Target amino acid sites in rt with codons and mutations leading to amino acid changes.



Title	Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
K32	AAG	Lys	AAG	Lys	GAG	Glu
N33	AAT	Asn	AAT	Asn	GAT	Asp
P34	CCT	Pro	ACT	Thr	GCT	Ala
H35	CAC	His	AAC	Asn	GAC	Asp
T37	ACC	Thr	ACC	Thr	GCC	Ala
P59	CCA	Pro	ACA	Thr	GCA	Ala
K60	AAA	Lys	AAA	Lys	GAA	Glu
F61	TTC	Phe	ATC	Ile	GTC	Val
A62	GCA	Ala	ACA	Thr	GCA	Ala
V63	GTC	Val	ATC	Ile	GTC	Val
D83	GAT	Asp	AAT	Asn	GAT	Asp
V84	GTG	Val	ATG	Met	GTG	Val
S85	TCT	Ser	ACT	Thr	GCT	Ala
A86	GCG	Ala	ACG	Thr	GCG	Ala
Y89	TAT	Tyr	AAT	Asn	GAT	Asp
H90	CAT	His	AAT	Asn	GAT	Asp
I/L91	ATT	Ile	ATT	Ile	GTT	Val
P177	CCG	Pro	ACG	Thr	GCG	Ala
F178	TTT	Phe	ATT	Ile	GTT	Val
L179	CTC	Leu	ATC	Ile	GTC	Val
L180	CTG	Leu	ATG	Met	GTG	Val
A181	TTG	Leu	ATG	Met	GTG	Val
Q183	CAG	Gln	AAG	Lys	GAG	Glu
F183	TTT	Phe	ATT	Ile	GTT	Val
T184	ACT	Thr	ACT	Thr	GCT	Ala
Y203	TAT	Tyr	AAT	Asn	GAT	Asp
M204	ATG	Met	ATG	Met	GTG	Val
L235	TTG	Leu	ATG	Met	GTG	Val
N236	AAC	Asn	AAC	Asn	GAC	Asp
T237	ACT	Thr	ACT	Thr	GCT	Ala
P237	CCT	Pro	ACT	Thr	GCT	Ala
N238	AAT	Asn	AAT	Asn	GAT	Asp
H238	CAC	His	AAC	Asn	GAC	Asp
A238	GCT	Ala	ACT	Thr	GCT	Ala
S239	TCT	Ser	ACT	Thr	GCT	Ala
Q238	CAG	Gln	AAG	Lys	GAG	Glu
K239	AAA	Lys	AAA	Lys	GAA	Glu
L247	CTT	Leu	ATT	Ile	GTT	Val
N248	AAC	Asn	AAC	Asn	GAC	Asp
H248	CAT	His	AAT	Asn	GAT	Asp
F249	TTC	Phe	ATC	Ile	GTC	Val
M250	ATG	Met	ATG	Met	GTG	Val
G251	GGT	Gly	AGT	Ser	GGT	Gly
V251	GTC	Val	ATC	Ile	GTC	Val

TABLE 13 continued (II)

Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
CAG	Gln	TAG	Stop	AAG	Lys
CAT	His	TAT	Tyr	AAT	Asn
CCT	Pro	TCT	Ser	CAT	His
CAC	His	TAC	Tyr	CAC	His
CCC	Pro	TCC	Ser	AAC	Asn
CCA	Pro	TCA	Ser	CAA	Gln
CAA	Gln	TAA	Stop	AAA	Lys
CTC	Leu	TTC	Phe	TAC	Tyr
CCA	Pro	TCA	Ser	GAA	Glu
CTC	Leu	TTC	Phe	GAC	Asp
CAT	His	TAT	Tyr	GAT	Asp
CTG	Leu	TTG	Leu	GAG	Glu
CCT	Pro	TCT	Ser	TAT	Tyr
CCG	Pro	TCG	Ser	GAG	Glu
CAT	His	TAT	Tyr	TAT	Tyr
CAT	His	TAT	Tyr	CAT	His
CTT	Leu	TTT	Phe	AAT	Asn
CCG	Pro	TCG	Ser	CAG	Gln
CTT	Leu	TTT	Phe	TAT	Tyr
CTC	Leu	TTC	Phe	CAC	His
CTG	Leu	TTG	Leu	CAG	Gln
CTG	Leu	TTG	Leu	TAG	Stop
CAG	Gln	TAG	Stop	CAG	Gln
CTT	Leu	TTT	Phe	TAT	Tyr
CCT	Pro	TCT	Ser	AAT	Asn
CAT	His	TAT	Tyr	TAT	Tyr
CTG	Leu	TTG	Leu	AAG	Lys
CTG	Leu	TTG	Leu	TAG	Stop
CAC	His	TAC	Tyr	AAC	Asn
CCT	Pro	TCT	Ser	AAT	Asn
CCT	Pro	TCT	Ser	CAT	His
CAT	His	TAT	Tyr	AAT	Asn
CAC	His	TAC	Tyr	CAC	His
CCT	Pro	TCT	Ser	GAT	Asp
CCT	Pro	TCT	Ser	TAT	Tyr
CAG	Gln	TAG	Stop	CAG	Gln
CAA	Gln	TAA	Stop	AAA	Lys
CTT	Leu	TTT	Phe	CAT	His
CAC	His	TAC	Tyr	AAC	Asn
CAT	His	TAT	Tyr	CAT	His
CTC	Leu	TTC	Phe	TAC	Tyr
CTG	Leu	TTG	Leu	AAG	Lys
CGT	Arg	TGT	Cys	GAT	Asp
CTC	Leu	TTC	Phe	GAC	Asp

TABLE 13 continued (III)

Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
AGG	Arg	ACG	Thr	ATG	Met
AGT	Ser	ACT	Thr	ATT	Ile
CGT	Arg	CCT	Pro	CTT	Leu
CGC	Arg	CCC	Pro	CTC	Leu
AGC	Ser	ACC	Thr	ATC	Ile
CGA	Arg	CCA	Pro	CTA	Leu
AGA	Arg	ACA	Thr	ATA	Ile
TGC	Cys	TCC	Ser	TTC	Phe
GGA	Gly	GCA	Ala	GTA	Val
GGC	Gly	GCC	Ala	GTC	Val
GGT	Gly	GCT	Ala	GTT	Val
GGG	Gly	GCG	Ala	GTG	Val
TGT	Cys	TCT	Ser	TTT	Phe
GGG	Gly	GCG	Ala	GTG	Val
TGT	Cys	TCT	Ser	TTT	Phe
CGT	Arg	CCT	Pro	CTT	Leu
AGT	Ser	ACT	Thr	ATT	Ile
CGG	Arg	CCG	Pro	CTG	Leu
TGT	Cys	TCT	Ser	TTT	Phe
CGC	Arg	CCC	Pro	CTC	Leu
CGG	Arg	CCG	Pro	CTG	Leu
TGG	Trp	TCG	Ser	TTG	Leu
CGG	Arg	CCG	Pro	CTG	Leu
TGT	Cys	TCT	Ser	TTT	Phe
AGT	Ser	ACT	Thr	ATT	Ile
TGT	Cys	TCT	Ser	TTT	Phe
AGG	Arg	ACG	Thr	ATG	Met
TGG	Trp	TCG	Ser	TTG	Leu
AGC	Ser	ACC	Thr	ATC	Ile
AGT	Ser	ACT	Thr	ATT	Ile
CGT	Arg	CCT	Pro	CTT	Leu
AGT	Ser	ACT	Thr	ATT	Ile
CGC	Arg	CCC	Pro	CTC	Leu
GGT	Gly	GCT	Ala	GTT	Val
TGT	Cys	TCT	Ser	TTT	Phe
CGG	Arg	CCG	Pro	CTG	Leu
AGA	Arg	ACA	Thr	ATA	Ile
CGT	Arg	CCT	Pro	CTT	Leu
AGC	Ser	ACC	Thr	ATC	Ile
CGT	Arg	CCT	Pro	CTT	Leu
TGC	Cys	TCC	Ser	TTC	Phe
AGG	Arg	ACG	Thr	ATG	Met
GGT	Gly	GCT	Ala	GTT	Val
GGC	Gly	GCC	Ala	GTC	Val



TABLE 13 continued (IV)

Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid	Codon	Amino Acid
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
CCA	Pro	CCG	Pro	CCC	Pro	CCT	Pro
CAA	Gln	CAG	Gln	CAC	His	CAT	His
ACA	Thr	ACG	Thr	ACC	Thr	ACT	Thr
CCA	Pro	CCG	Pro	CCC	Pro	CCT	Pro
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
GCA	Ala	GCG	Ala	GCC	Ala	GCT	Ala
GTA	Val	GTG	Val	GTC	Val	GTT	Val
GAA	Glu	GAG	Glu	GAC	Asp	GAT	Asp
GTA	Val	GTG	Val	GTC	Val	GTT	Val
TCA	Ser	TCG	Ser	TCC	Ser	TCT	Ser
GCA	Ala	GCG	Ala	GCC	Ala	GCT	Ala
TAA	Stop	TAG	Stop	TAC	Tyr	TAT	Tyr
CAA	Gln	CAG	Gln	CAC	His	CAT	His
ATA	Ile	ATG	Met	ATC	Ile	ATT	Ile
CCA	Pro	CCG	Pro	CCC	Pro	CCT	Pro
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
CTA	Leu	CTG	Leu	CTC	Leu	CTT	Leu
CTA	Leu	CTG	Leu	CTC	Leu	CTT	Leu
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
CAA	Gln	CAG	Gln	CAC	His	CAT	His
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
ACA	Thr	ACG	Thr	ACC	Thr	ACT	Thr
TAA	Stop	TAG	Stop	TAC	Tyr	TAT	Tyr
ATA	Ile	ATG	Met	ATC	Ile	ATT	Ile
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
ACA	Thr	ACG	Thr	ACC	Thr	ACT	Thr
CCA	Pro	CCG	Pro	CCC	Pro	CCT	Pro
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
CAA	Gln	CAG	Gln	CAC	His	CAT	His
GCA	Ala	GCG	Ala	GCC	Ala	GCT	Ala
TCA	Ser	TCG	Ser	TCC	Ser	TCT	Ser
CAA	Gln	CAG	Gln	CAC	His	CAT	His
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
CTA	Leu	CTG	Leu	CTC	Leu	CTT	Leu
AAA	Lys	AAG	Lys	AAC	Asn	AAT	Asn
CAA	Gln	CAG	Gln	CAC	His	CAT	His
TTA	Leu	TTG	Leu	TTC	Phe	TTT	Phe
ATA	Ile	ATG	Met	ATC	Ile	ATT	Ile
GGA	Gly	GGG	Gly	GGC	Gly	GGT	Gly
GTA	Val	GTG	Val	GTC	Val	GTT	Val

**TABLE 14** Amino acid mutations at target sites in rt

Target	Mutation
K32	M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L
N33	D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R
P34	S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F
H35	I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G
T37	W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S
P59	S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F
K60	M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L
F61	P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M
A62	R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V
V63	A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y
D83	C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N
V84	A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y
S85	T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P
A86	R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V
Y89	V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W
H90	I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G
I/L91	K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H
P177	S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F
F178	P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M
L179	K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I
L180	K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I
A181	R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V
Q183	E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C
F183	P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M
T184	W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S
Y203	V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W
M204	F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K
L235	K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I
N236	D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R
T237	W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S
P237	S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F
N238	D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R
H238	I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G
A238	R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V
S239	T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P
Q238	E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C
K239	M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L
L247	K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I
N248	D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R
H248	I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G

Target	Mutation
F249	P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M
M250	F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K
G251	H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E
V251	A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y

TABLE 15 Summary of HBV mutations in Patient F treated with ADV

Sample Name	Genotype	Polymerase*	Surface
CAP 01564808	A	rtL157L/M rtA181V rtV207I rtN236T	sF83S sL173F sW199L

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\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

\*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 16** Summary of HBV mutations in Patient G treated with ADV

Sample Name	Genotype	Polymerase*	Surface
KAN 02510355	C	rtL80V rtP109S rtI163V <b>rtM204I</b> rtL229M <b>rtN/H/A/S/Q238K</b>	sI126T sK160R sS174N sA184V sW196L sS210N <b>sF/C220L</b> sY221C

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

5 \*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 17** Summary of HBV mutations in Patient H treated with ADV

Sample Name	Genotype	Polymerase*	Surface
LAV0303	D	rtS78S/T rtN118N/S rtN139N/K rtV142E rtA181A/T rtI204M rtQ/P/S/Stop215Q rtE218K/E rtN238N/H	sC69Stop/C sC76Y sI110V/I sY134N sW172Stop/W sW196Stop sS207R

10

\* Nomenclature according to Stuyver *et al.*, 2001, *supra*.

\*\* Mutations in bold have not been detected in reference HBV genotypes, mutations not in bold are changes from the previous sample that are present in reference genotypes.

**TABLE 18** *In vitro* drug susceptibility of the HBV reference laboratory strain and patient-derived HBV isolate

Mutation	<i>In vitro</i> Susceptibility		
	IC <sub>50</sub> (fold change from wild-type)		
	Real-time PCR	Southern Blot	
	Adefovir	Adefovir	Lamivudine
Wild-type (pPC)	1	1	1
rt N236T/N238D	23	NA <sup>1</sup>	NA <sup>1</sup>
rt A181T/N236T/N238D	5.1	7.3	>100
rt L180M/M204V <sup>2</sup>	NT <sup>5</sup>	0.9	>2500

5 <sup>1</sup> NA, not analyzed.

<sup>2</sup> Data from Delaney *et al.*, 2001, *supra*

10 Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features

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## CLAIMS

1. An isolated HBV variant wherein said variant comprises a nucleoside mutation in a gene encoding a DNA polymerase resulting in at least one amino acid addition, substitution and/or deletion to said DNA polymerase and wherein said variant exhibits decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combinations thereof
2. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV.
3. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to both LMV.
4. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to TFV.
5. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to FTC.
6. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and LMV.
7. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and TFV.
8. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to LMV and TFV.



9. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and FTC.
10. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to LMV and FTC.
11. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to TFV and FTC.
12. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and LMV and TFV.
13. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and LMV and FTC.
14. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to FTC and LMV and TFV.
15. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and FTC and TFV.
16. The isolated HBV variant of Claim 1 wherein said variant exhibits decreased sensitivity to ADV and LMV and TFV and FTC.
17. The isolated HBV variant of any one of Claims 1 to 16 wherein said variant exhibits reduced interactivity to an immunological reagent specific to HBsAg.
18. The isolated HBV variant of Claim 1 wherein said variant comprises a mutation in domain F of the HBV DNA polymerase thereby conferring an altered amino acid sequence to the sequence set forth in Formula I [SEQ ID NO:1]:

# FORMULA I

L, X<sub>1</sub>, X<sub>2</sub>, D, W, G, P, C, X<sub>3</sub>, X<sub>4</sub>, H, G, X<sub>5</sub>, H, X<sub>6</sub>, I, R, X<sub>7</sub>, P, R, T, P, X<sub>8</sub>, R, V, X<sub>9</sub>, G, G, V, F, L, V, D, K, N, P, H, N, T, X<sub>10</sub>, E, S, X<sub>11</sub>, L, X<sub>12</sub>, V, D, F, S, Q, F, S, R, G, X<sub>13</sub>, X<sub>14</sub>, X<sub>15</sub>, V, S, W, P, K, F, A, V, P, N, L, X<sub>16</sub>, S, L, T, N, L, L, S\*

wherein:

- X<sub>1</sub> is L or R or I;
- X<sub>2</sub> is E or D;
- X<sub>3</sub> is T or D or A or N or Y;
- X<sub>4</sub> is E or D;
- X<sub>5</sub> is E or K or Q;
- X<sub>6</sub> is H or R or N;
- X<sub>7</sub> is I or T;
- X<sub>8</sub> is A or S;
- X<sub>9</sub> is T or R;
- X<sub>10</sub> is A or T or S;
- X<sub>11</sub> is R or T;
- X<sub>12</sub> is V or G;
- X<sub>13</sub> is S or I or T or N or V;
- X<sub>14</sub> is T or S or H or Y;
- X<sub>15</sub> is R or H or K or Q;
- X<sub>16</sub> is Q or P;

and wherein S\* is designated as amino acid 74.

19. The isolated HBV variant of Claim 1 wherein said variant comprises a mutation in any one of domains A through E thereby conferring an altered amino acid sequence to the sequence set forth in Formula II [SEQ ID NO:2]:

## FORMULA II

SX<sub>1</sub>LSWLSLDVSAAFYHX<sub>2</sub>PLHPAAMPHELLX<sub>3</sub>GSSGLX<sub>4</sub>RYV  
ARLSSX<sub>5</sub>SX<sub>6</sub>X<sub>7</sub>XNX<sub>8</sub>QX<sub>9</sub>X<sub>10</sub>XXXXX<sub>11</sub>LHX<sub>12</sub>X<sub>13</sub>CSRX<sub>14</sub>LYVSLX<sub>15</sub>  
LLYX<sub>16</sub>TX<sub>17</sub>GX<sub>18</sub>KLHLX<sub>19</sub>X<sub>20</sub>HPIX<sub>21</sub>LGFRKX<sub>22</sub>PMGX<sub>23</sub>GLSPFL  
LAQFTSAIX<sub>24</sub>X<sub>25</sub>X<sub>26</sub>X<sub>27</sub>X<sub>28</sub>RAFX<sub>29</sub>HCTX<sub>30</sub>X<sub>31</sub>FX<sub>32</sub>YM\*DDX<sub>33</sub>VLGA  
X<sub>34</sub>X<sub>35</sub>X<sub>36</sub>X<sub>37</sub>HX<sub>38</sub>EX<sub>39</sub>LX<sub>40</sub>X<sub>41</sub>X<sub>42</sub>X<sub>43</sub>X<sub>44</sub>X<sub>45</sub>X<sub>46</sub>LLX<sub>47</sub>X<sub>48</sub>GIHLNPX<sub>49</sub>K  
TKRWGYSLNFMGYX<sub>50</sub>IG

wherein:

- X is any amino acid
- X<sub>1</sub> is N or D;
- X<sub>2</sub> is I or P;
- X<sub>3</sub> is I or V;
- X<sub>4</sub> is S or D;
- X<sub>5</sub> is T or N;
- X<sub>6</sub> is R or N;
- X<sub>7</sub> is N or I;
- X<sub>8</sub> is N or Y or H;
- X<sub>9</sub> is H or Y;
- X<sub>10</sub> is G or R;
- X<sub>11</sub> is D or N;
- X<sub>12</sub> is D or N;
- X<sub>13</sub> is S or Y;
- X<sub>14</sub> is N or Q;
- X<sub>15</sub> is L or M;
- X<sub>16</sub> is K or Q;
- X<sub>17</sub> is Y or F;
- X<sub>18</sub> is R or W;

X<sub>19</sub> is Y or L;  
X<sub>20</sub> is S or A;  
X<sub>21</sub> is I or V;  
X<sub>22</sub> is I or L;  
X<sub>23</sub> is V or G;  
X<sub>24</sub> is C or L;  
X<sub>25</sub> is A or S;  
X<sub>26</sub> is V or M;  
X<sub>27</sub> is V or T;  
X<sub>28</sub> is R or C;  
X<sub>29</sub> is F or P;  
X<sub>30</sub> is L or V;  
X<sub>31</sub> is A or V;  
X<sub>32</sub> is S or A;  
X<sub>33</sub> is V or L or M;  
X<sub>34</sub> is K or R;  
X<sub>35</sub> is S or T;  
X<sub>36</sub> is V or G;  
X<sub>37</sub> is Q or E;  
X<sub>38</sub> is L or S or R;  
X<sub>39</sub> is S or F;  
X<sub>40</sub> is F or Y;  
X<sub>41</sub> is T or A;  
X<sub>42</sub> is A or S;  
X<sub>43</sub> is V or I;  
X<sub>44</sub> is T or C;  
X<sub>45</sub> is N or S;  
X<sub>46</sub> is F or V;  
X<sub>47</sub> is S or D;  
X<sub>48</sub> is L or V;  
X<sub>49</sub> is N or Q;

X<sub>50</sub> is V or I; and  
M\* is amino acid 204;

and wherein the first S is designated as amino acid 75.

20. The isolated HBV variant of Claim 18 or 19 wherein said variant further comprises an altered HBsAg.
21. An isolated HBV variant comprising a mutation in the nucleotide sequence encoding HBsAg resulting in an amino acid addition, substitution and/or deletion in said HBsAg in a region corresponding to the amino acid sequence set forth in SEQ ID NO:1 or SEQ ID NO:2 and wherein said variant exhibits decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combinations thereof.
22. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV.
23. The isolated HBV variant of Claim 21 wherein said variants exhibits decreased sensitivity to LMV.
24. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to TFV.
25. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to FTC.
26. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased

sensitivity to ADV and LMV.

27. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to LMV and TFV.

28. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and FTC.

29. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to LMV and FTC.

30. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to TFV and FTC.

31. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and TFV.

32. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and LMV and TFV.

33. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and LMV and FTC.

34. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to FTC and LMV and TFV.

35. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and FTC and TFV.

36. The isolated HBV variant of Claim 21 wherein said variant exhibits decreased sensitivity to ADV and LMV and TFV and FTC.

37. The isolated HBV variant of Claim 21 wherein an antibody specific for a wild-type HBsAg exhibits a reduced capacity to neutralize said HBV variant and wherein said HBV variant is selected by exposure of a subject to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, in single or combinations or sequential therapy.
38. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtS21A, rtL122F, rtN124H, rtT28N, rtP130Q, rtD131N and rtY135C or a combination thereof or an equivalent mutation.
39. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M or a combination thereof or an equivalent mutation.
40. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D or a combination thereof or an equivalent mutation.
41. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtH90D and rtL/F108L or a combination thereof or an equivalent mutation.
42. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtL157L/M, rtA181V and rtV207I or a combination thereof or an equivalent mutation.
43. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV

DNA polymerase selected from rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K or a combination thereof or an equivalent mutation.

44. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the surface antigen selected from sP120T, sM125F and sT127A or a combination thereof or an equivalent mutation.

45. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the surface antigen selected from sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C or a combination thereof or an equivalent mutation.

46. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the surface antigen selected from sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop or a combination thereof or an equivalent mutation.

47. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV surface antigen selected from sI81M and sP214Q or a combination thereof or an equivalent mutation.

48. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV surface antigen selected from sF83S, sL173F and sW199L or a combination thereof or an equivalent mutation.

49. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV surface antigen selected from sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C or a combination thereof or an equivalent mutation.

50. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV surface antigen selected from sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R or a combination thereof or an equivalent mutation.



51. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtK32, rtN33, rtP34, rtH35 and rtT37 or a combination thereof or an equivalent mutation.
52. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtP59, rtK60, rtF61, rtA62 and rtV63 or a combination thereof or an equivalent mutation.
53. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91 or a combination thereof or an equivalent mutation.
54. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184 or a combination thereof or an equivalent mutation.
55. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtM204 and rtY203 or a combination thereof or an equivalent mutation.
56. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rt235, rt236, rt237, rt238 and rt239 or a combination thereof or an equivalent mutation.
57. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rt247, rt248, rt249, rt250 and rt251 or a combination thereof or an equivalent mutation.
58. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion; N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;

P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;

A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion.

59. A method for determining the potential for an HBV to exhibit reduced sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV or optionally other nucleoside analogs or other anti-HBV agents, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in any one or more of domains F and A through E or a region proximal thereto of said DNA polymerase and associated with resistance or decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, wherein the presence of such a mutation is an indication of the likelihood of resistance to said ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV.

60. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to

ADV.

61. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to LMV.
62. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to TFV.
63. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to FTC.
64. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and LMV.
65. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and TFV.
66. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to LMV and TFV.
67. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and FTC.
68. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to TFV and FTC.
69. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to LMV and FTC.
70. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and LMV and TFV.
71. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV

and LMV and FTC.

72. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to LMV and TFV and FTC.

73. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and FTC and TFV.

74. The method of Claim 59 wherein the HBV exhibits reduced sensitivity to ADV and LMV and TFV and FTC.

75. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtS21A, rtL122F, rtN124H, rtT28N, rtP130Q, rtD131N and rtY135C or a combination thereof or an equivalent mutation.

76. The isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M or a combination thereof or an equivalent mutation.

77. The isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D or a combination thereof or an equivalent mutation.

78. The isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A or a combination thereof or an equivalent mutation.

79. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtH90D and rtL/F108L or a combination thereof or an equivalent mutation.

80. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtL157L/M, rtA181V and rtV207I or a combination thereof or an equivalent mutation.

81. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K or a combination thereof or an equivalent mutation.

82. The isolated HBV variant of Claim 1 or 37 comprising a mutation in the DNA polymerase selected from rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H or a combination thereof or an equivalent mutation.

83. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the surface antigen gene selected from sP120T, sM125F and sT127A or a combination thereof or an equivalent mutation.

84. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV Surface antigen gene selected from sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C or a combination thereof or an equivalent mutation.

85. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the surface antigen selected from sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop or a combination thereof or an equivalent mutation.

86. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA surface antigen selected from sN40S, sC69Stop, sM75I,

sL88P, sT118A, sW182Stop, sW196L, sY206H and sY225F or a combination thereof or an equivalent mutation.

87. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA surface antigen selected from sI81M and sP214Q or a combination thereof or an equivalent mutation.

88. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA surface antigen selected from sF83S, sL173F and sW199L or a combination thereof or an equivalent mutation.

89. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA surface antigen selected from sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C or a combination thereof or an equivalent mutation.

90. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA surface antigen selected from sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R or a combination thereof or an equivalent mutation.

91. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtK32, rtN33, rtP34, rtH35 and rtT37 or a combination thereof or an equivalent mutation.

92. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtP59, rtK60, rtF61, rtA62 and rtV63 or a combination thereof or an equivalent mutation.

93. An isolated DNA molecule from an HBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtD83, rtV84, rtS85, rtA86, rtY89,

rtH90 and rtI/L91 or a combination thereof or an equivalent mutation.

94. An isolated DNA molecule from anHBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184 or a combination thereof or an equivalent mutation.

95. An isolated DNA molecule from anHBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rtM204 and rtY203 or a combination thereof or an equivalent mutation.

96. An isolated DNA molecule from anHBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rt235, rt236, rt237, rt238 and rt239 or a combinations thereof or an equivalent mutation.

97. An isolated DNA molecule from anHBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from rt247, rt248, rt249, rt250 and rt251 or a combinations thereof or an equivalent mutation.

98. An isolated DNA molecule from anHBV variant of Claim 1 or 37 comprising a mutation in the HBV DNA polymerase selected from  
K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;



V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;

G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion.

99. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtS21A, rtL122F, rtN124H, rtT28N, rtP130Q, rtD131N and rtY135C or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

100. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

101. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and

LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

102. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and optionally other nucleoside analogs.

103. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtH90D and rtL/F108L or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

104. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtL157L/M, rtA181V and rtV207I or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and

optionally other nucleoside analogs.

105. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

106. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

107. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sP120T, sM125F and sT127A or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally

other nucleoside analogs.

108. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

109. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

110. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sN40S, sC69Stop, sM75I, sL88P, sT118A, sW182Stop, sW196L, sY206H and sY225F or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

111. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of s181M and sP214Q or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

112. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sF83S, sL173F and sW199L or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

113. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

114. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

115. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtK32, rtN33, rtP34, rtH35 and rtT37 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

116. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtP59, rtK60, rtF61, rtA62 and rtV63 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

117. A method for determining whether an HBV strain exhibits reduced sensitivity

to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

118. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

119. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rtM204 and rtY203 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

120. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA



from said HBV and screening for a mutation wherein the presence of rt235, rt236, rt237, rt238 and rt239 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

121. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of rt247, rt248, rt249, rt250 and rt251 or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside analogs.

122. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation wherein the presence of K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;

D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/YV/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;

M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;

G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and

V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and optionally other nucleoside analogs.

123. A method for detecting an agent which exhibits inhibitory activity to an HBV which exhibits resistance or decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and optionally other nucleoside or nucleotide analogs or other anti-HBV agents, said method comprising:

generating a genetic construct comprising a replication competent-effective amount of the genome from said HBV contained in a plasmid vector and then transfecting said cells with said construct;

contacting said cells, before, during and/or after transfection, with the agent to be tested;

culturing said cells for a time and under conditions sufficient for the HBV to replicate, express genetic sequences and/or assemble and/or release virus or virus-like particles if resistant to said agent; and

subjecting the cells, cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed genetic material and/or assembled and/or been released in the presence of said agent.

124. A method for detecting an agent which exhibits inhibitory activity to an HBV which exhibits resistance or decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV, and optionally other nucleoside or nucleotide analogs or other anti-HBV agents, said method comprising:

generating a genetic construct comprising a replication competent-effective amount of the genome from said HBV contained in or fused to an amount of a baculovirus genome effective to infect cells and then infecting said cells with said construct;

contacting said cells, before, during and/or after infection, with the agent to be tested;

culturing said cells for a time and under conditions sufficient for the HBV to replicate, express genetic sequences and/or assemble and/or release virus or virus-like particles if resistant to said agent; and

subjecting the cells, cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed genetic material and/or assembled and/or been released in the presence of said agent.

125. The method of Claim 123 or 124 wherein the HBV genome is stably integrated into the cells' genome.

126. An agent identified by the method of any one of Claims 123 to 124.

127. Use of an HBV variant according to any one of Claims 1 to 59 or a component thereof in the rational design of an anti-HBV agent.

128. Use according to Claim 126 wherein the rational design comprises microarray analysis.
129. Use according to Claim 126 wherein the rational design is based on the crystal structure or NMR structure of a viral component.
130. A vaccine comprising an antigenic component of the HBV variant of any one of Claims 1 to 59 or an antigenic component thereof or an antibody thereto.
131. The vaccine of Claim 130 wherein the antigenic component is an HBsAg or PreS1 or PreS2.
132. The vaccine of Claim 130 wherein the antigenic component is a defective HBV variant.
133. The vaccine of Claim 130 comprising an antibody to HBsAg or PreS1 or PreS2.
134. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtS21A, rtL122F, rtN124H, rtT28N, rtP130Q, rtD131N and rtY135C.
135. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V and rtI235I/M.
136. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F.

137. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D.

138. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A.

139. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtH90D and rtL/F108L.

140. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtL157L/M, rtA181V and rtV207I.

141. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtL80V, rtP109S, rtI163V, rtL229M and rtN/H/A/S/Q238K.

142. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E and rtN238N/H.

143. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sP120T, sM125F and sT127A.

144. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sT118R, sM133T, sF134V, sI195M, sS207R and sY225Y/C.

145. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sS126T, sM133L/M, sS143S/T, sD144A, sG145A and sW172Stop.
146. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sN40S, sC69Stop, sM75I, sL88P, sT118A, sW182Stop, sW196L, sY206H and sY225F.
147. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sI81M and sP214Q.
148. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sF83S, sL173F and sW199L.
149. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C.
150. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from sC69Stop/C, sC76Y, sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R.
151. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtK32, rtN33, rtP34, rtH35 and rtT37.
152. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtP59, rtK60, rtF61, rtA62 and rtV63.
153. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 and rtI/L91.

154. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184.

155. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rtM204 and rtY203.

156. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rt235, rt236, rt237, rt238 and rt239.

157. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from rt247, rt248, rt249, rt250 and rt251.

158. The vaccine of Claim 130 wherein the HBV or its antigenic compound is from an HBV variant having a mutation selected from,

K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion;  
V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion;  
S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;



H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion;  
P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and  
V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion.

159. A computer product for assessing the likely usefulness of a viral variant or biological sample comprising same for determining an appropriate therapeutic protocol in a subject, said product comprising:

- (1) code that receives as input index values ( $I_V$ s) for at least two features associated with said viral agents or biological sample comprising same, wherein said features are selected from:
  - (a) the ability to exhibit resistance for reduced sensitivity to a particular compound or immunological agent;
  - (b) an altered DNA polymerase from wild-type HBV;
  - (c) an altered surface antigen from wild-type HBV;
  - (d) morbidity or recovery potential of a patient; or
  - (e) altered replication capacity (increased or decreased);
- (2) code that adds said  $I_V$ s to provide a sum corresponding to a potency value ( $P_V$ ) for said viral variants or biological samples; and
- (3) a computer readable medium that stores the codes.

160. A computer for assessing the likely usefulness of a viral variant or biological sample comprising same in a subject, wherein said computer comprises:

- (1) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said machine-readable data comprise  $I_V$ s for at least two features associated with said viral variant or biological sample; wherein said features are selected from:-
  - (a) the ability to exhibit resistance for reduced sensitivity to a particular compound or immunological agent;

- (b) an altered DNA polymerase from wild-type HBV;
  - (c) an altered surface antigen from wild-type HBV;
  - (d) morbidity or recovery potential of a patient; or
  - (e) altered replication capacity (increased or decreased);
- (2) a working memory for storing instructions for processing said machine-readable data;
- (3) a central-processing unit coupled to said working memory and to said machine-readable data storage medium, for processing said machine readable data to provide a sum of said  $I_{Vs}$  corresponding to a  $P_V$  for said compound(s); and
- (4) an output hardware coupled to said central processing unit, for receiving said  $P_V$ .

161. A composition comprising an agent capable of directly or indirectly inhibiting an HBV variant as defined in any one of Claims 1 to 59, said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.

162. The composition of Claim 161 wherein the agent is a recombinant protein from said HBV variant.

163. The composition of Claim 161 wherein the recombinant protein is HBsAg or PreS1 or PreS2.

164. The composition of Claim 161 wherein the agent is capable of inhibiting an HBV variant polymerase.

165. The composition of Claim 161 wherein the agent is identified by natural product screening or rational drug design.

166. The composition of Claim 161 wherein the agent is a defective HBV variant.
167. The composition of Claim 161 wherein the agent is an antibody directed to an HBV compound.
168. The composition of Claim 161 wherein the agent is a ribozyme, antisense molecule or sense molecule relative to an HBV gene.
169. A method according to Claims 37 to 57 wherein a virus related to HBV from the family of hepadnaviruses such as WHV or DHBV exhibits reduced sensitivity to a nucleoside analog, said method comprising isolating DNA or corresponding mRNA from said HBV, or DHBV or WHV and screening for a mutation or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV.
170. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.
171. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA

or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sP120T, sM125T and sT127A selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

172. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sT118R, sM133T, sF134V sI195M, sS207R and sY225Y/C selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

173. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sS126T, sM133L/M, sS143S/T, sD144A sG145A and sW172Stop selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

174. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sN40S, and sC69 Stop, sM75I, sL88P, sT118A, sW182stop, sW196L, sY206H and sY225F selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

175. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sF83S, sL173F and sW199L selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

176. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and

LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

177. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from sC69Stop/C, sC76Y sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

178. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

179. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtS21A, rtL122F, rtN124H, rtH126R,

rtT128N, rtP130Q, rtD131N, rtY135C selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

180. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtN/S/T/I/V53D, rtY126Q, rtL180M, rtS202G, rtI204V, rtI235I/M selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

181. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtN53D, rtY54H, rtS57P, rtL91I, rtS116P, rtF122L, rtY124H, rtV134D, rtY141Y/F, rtL145M, rtF151F/Y, rtA181T, rtK212R, rtL217R, rtS219A, rtN236T and rtN238D selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.



182. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtS78T, rtV84M, rtY126C, rtV191I, rtM204I and rtV214A selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

183. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtH90D and rtL/F108L selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

184. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtL157L/M, rtA181V, rtV207I; and rtN236T selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing

interactivity of said antibodies to said mutated surface antigen.

185. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtL80V, rtP109S, rtI163V, rtM204I, rtL229M and rtN/H/A/S/Q238K selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

186. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtS78S/T, rtN118N/S, rtN139N/K, rtV142E, rtA181A/T, rtI204M, rtQ/P/S/Stop215Q, rtE218K/E, and rtN238N/H selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

187. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtK32, rtN33, rtP34, rtH35 and rtT37 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV,

LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

188. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtP59, rtK60, rtF61, rtA62 and rtV63 elected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

189. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtD83, rtV84, rtS85, rtA86, rtY89, rtH90 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

190. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the

presence of such a mutation is selected from rtP177, rtF178, rtL179, rtL180, rtA181, rtQ182, rtF183 and rtT184 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

191. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rtM204 and rtY203 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV; ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

192. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rt235, rt236, rt237, rt238 and rt239 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

193. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA

or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation is selected from rt247, rt248, rt249, rt250 and rt251 selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

194. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV surface antigen and/or HBV DNA polymerase genes wherein the presence of such a mutation, K32M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion; N33D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion; P34S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion; H35I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion; T37W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion; P59S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion; K60M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion; F61P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion; A62R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion; V63A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion; D83C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/deletion; V84A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion; S85T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion; A86R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion; Y89V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion; H90I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion; I/L91K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/deletion; P177S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;

F178P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
L179K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
L180K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
A181R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
Q183E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
F183P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
T184W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
Y203V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/deletion;  
M204F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
L235K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N236D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
T237W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/deletion;  
P237S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/deletion;  
N238D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H238I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
A238R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/deletion;  
S239T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/deletion;  
Q238E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/deletion;  
K239M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/deletion;  
L247K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/deletion;  
N248D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/V/A/R/deletion;  
H248I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/deletion;  
F249P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/M/deletion;  
M250F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/G/H/I/L/K/deletion;  
G251H/I/L/K/M/F/P/S/T/W/Y/V/A/R/N/D/C/Q/E/deletion; and

V251A/R/N/D/C/Q/E/G/H/I/L/K/M/F/P/S/T/W/Y/deletion, is selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

195. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV and is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

196. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation is selected from sP120T, sM125T and sT127A selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

197. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected from sT118R, sM133T, sF134V sI195M, sS207R and sY225Y/C selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

198. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected from sS126T, sM133L/M, sS143S/T, sD144A sG145A and sW172Stop selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

199. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected from sN40S, and sC69 Stop, sM75I, sL88P, sT118A, sW182stop, sW196L, sY206H and sY225F selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

200. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected from sF83S, sL173F and sW199L selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen



201. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected from sI126T, sK160R, sS174N, sA184V, sW196L, sS210N, sF/C220L and sY221C selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

202. A method for determining the potential for an HBV to exhibit reduced interactivity to antibody to HBV surface antigen, said method comprising isolated protein from said HBV encoding HBV surface antigen wherein the presence of such a mutation was selected sC69Stop/C, sC76Y sI110V/I, sY134N, sW172Stop/W, sW196Stop and sS207R selected during treatment with ADV, LMV, TFV, or FTC, or ADV and LMV, ADV and TFV, LMV and TFV, FTC and ADV, FTC and TFV, FTC and LMV, or ADV and LMV and TFV, or ADV and FTC and TFV, TFV and FTC and LMV, ADV and LMV and FTC, or ADV and FTC and LMV and TFV is an indication of the likelihood of reducing interactivity of said antibodies to said mutated surface antigen.

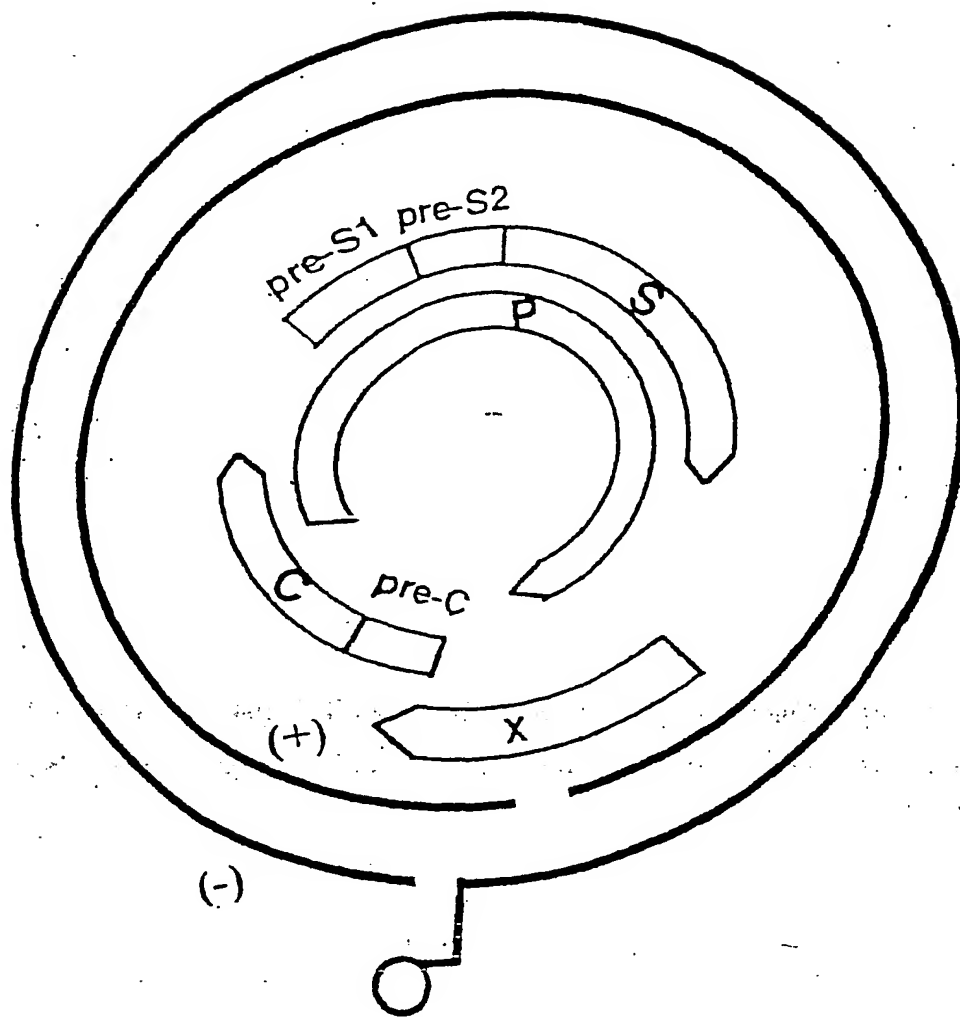


Figure 1

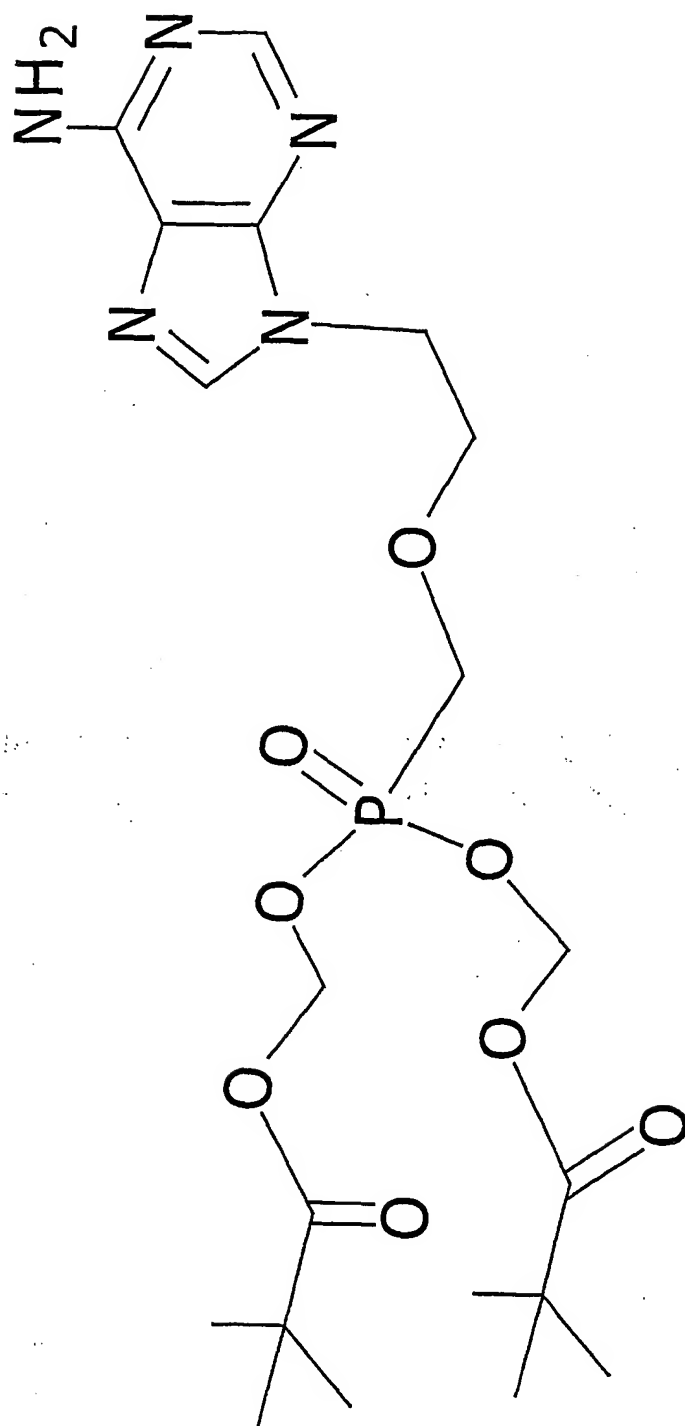
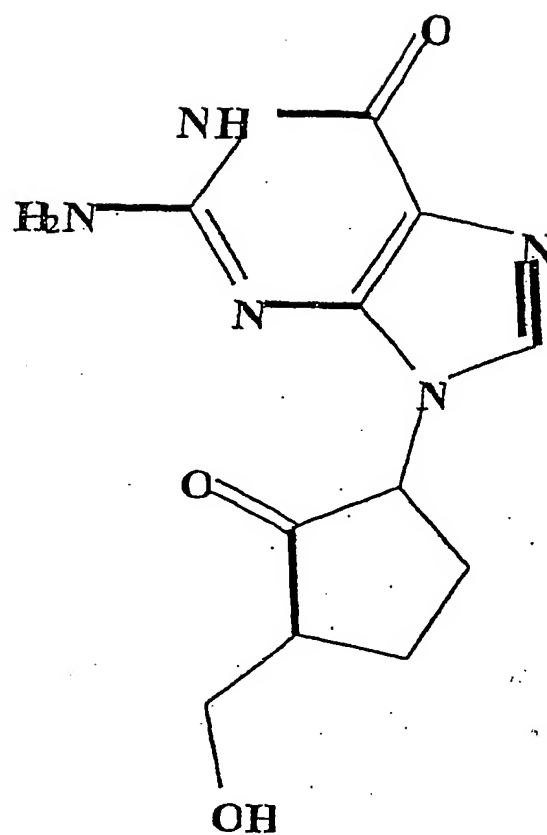


Figure 2



**Figure 3**



IL1A1 F, A-E	781	TGGCTCAGTTTACTAGTGGCCATTGTTTCAGTGGTTCGTTAGGGCTTCCCCCACTGTTGGCTTTCAGTTATATGATGATGGTATTTGGGGCCCAAGTC	880	[SEQ ID NO:8]
IL1A2 F, A-E	789	TGGCTCAGTTTACTAGTGGCCATTGTTTCAGTGGTTCGTTAGGGCTTCCCCCACTGTTGGCTTTCAGTTATATGATGATGGTATTTGGGGCCCAAGTC	888	[SEQ ID NO:9]
IL1A3 F, A-E	801	TGGCTCAGTTTACTAGTGGCCATTGTTTCAGTGGTTCGTTAGGGCTTCCCCCACTGTTGGCTTTCAGTTATATGATGATGGTATTTGGGGCCCAAGTC	900	[SEQ ID NO:10]
IL1A4 F, A-E	774	TGGCTCAGTTTACTAGTGGCCATTGTTTCAGTGGTTCGTTAGGGCTTCCCCCACTGTTGGCTTTCAGTTATATGATGATGGTATTTGGGGCCCAAGTC	873	[SEQ ID NO:11]
IL1A1 F, A-E	881	TGTAYAGCAYCTTGAGTCCCTTTTACCGCTGTTACCAATTTCTTTTGGTATATACATTTAAACCCCTAACAAACTTAAAGATGGGTTACTCT	980	
IL1A2 F, A-E	889	TGTACAGCATCTTGAGTCCCTTTTACCGCTGTTACCAATTTCTTTTGGTATATACATTTAAACCCCTAACAAACTTAAAGATGGGTTACTCT	988	
IL1A3 F, A-E	901	TGTACAGCATCTTGAGTCCCTTTTACCGCTGTTACCAATTTCTTTTGGTATATACATTTAAACCCCTAACAAACTTAAAGATGGGTTACTCT	1000	
IL1A4 F, A-E	874	TGTACAGCATCTTGAGTCCCTTTTACCGCTGTTACCAATTTCTTTTGGTATATACATTTAAACCCCTAACAAACTTAAAGATGGGTTACTCT	973	
IL1A1 F, A-E	981	TTACATTTTCANGGNTATGTCATTTGGATGTTATGGTCAATGTCACAGATCATCATACAGAAAATCAAAGATGGTTT	1060	
IL1A2 F, A-E	989	CTAAATTTTATGGTTATGTCATTTGGATGTTATGGTCCCTTG	1030	
IL1A3 F, A-E	1001	CTAAATTTTATGGTTATGTCATTTGGATGTTATGGTCCCTTG	1077	
IL1A4 F, A-E	974	TTAAATTTTCATGGGATATGTCATTTGGATGTTATGGG	1010	

Figure 4 (continued)

## Figure 5

## Patient A HBsAg Amino acid alignment

[illegible]

## Figure 6



	10	20	30	40	50	
S0						[SEQ ID NO:20]
S6						[SEQ ID NO:21]
S8					T	[SEQ ID NO:22]
S12	TTTTGGGGAGCCCTCAGGCTCAGGGCATATTACAAACTCTGCCAGCAAAT					[SEQ ID NO:23]
S15				TACAAACTTTGCCAGCAAAT		[SEQ ID NO:24]

	60	70	80	90	100	
S0						
S6						
S8	GCCCCCTTCTGCCTCCACCAATCGCCAGTCAGGAAGGCAGCCTACCCCGCT					
S12	CCACCTCCTGCCTCCACCAATCGCCAGTCAGGAAGGCAGCCTACCCCGCT					
S15	CCACCTCCTGCCTCCACCAATCGCCAGTCAGGAAGGCAGCCTACCCCGCT					

	110	120	130	140	150	
S0						
S6						
S8	GTCTCCACCTTTGAGAGACACTCATCCTCAGGCCATGCAGTGGAACCTCAA					
S12	GTCTCCACCTTTGAGAGACACTCATCCTCAGGCCATGCAGTGGAACCTCAA					
S15	GTCTCCACCTTTGAGAGACACTCATCCTCAGGCCATGCAGTGGAACCTCAA					

	160	170	180	190	200	
S0						
S6						
S8	CAACCTTCCACCAAACCTCTGCAAGATCCCAGAGTGAAAGGCCTGTATTTTC					
S12	CAACCTTCCACCAAACCTCTGCAAGATCCCAGAGTGAAAGGCCTGTATTTTC					
S15	CAACCTTCCACCAAACCTCTGCAAGATCCCAGAGTGAAAGGCCTGTATTTTC					

	210	220	230	240	250	
S0						
S6						
S8	CCTGCTGGTGGCTCCAGTTCAGGAACAGTAAACCCTGTTCCGACTACTGC					
S12	CCTGCTGGTGGCTCCAGTTCAGGAACAGTAAACCCTGTTCCGACTACTGC					
S15	CCTGCTGGTGGCTCCAGTTCAGGAACAGTAAACCCTGTTCCGACTACTGC					

	260	270	280	290	300	
S0						
S6						
S8	CTCTCACTCATCGTCAATCTTCTCGAGGATTGGGGTCCCTGCGCTGAACA					
S12	CTCTCACTCATCGTCAATCTTCTCGAGGATTGGGGTCCCTGCGCTGAACA					
S15	CTCTCACTCATCGTCAATCTTCTCGAGGATTGGGGTCCCTGCGCTGAACA					

Figure 7

	310	320	330	340	350
S0					
S6					
S8	TGGAGAACATCACATCAGGACTCCTAGGACCCCTTCTCGTGTTACAGGCG				
S12	TGGAGAACATCACATCAGGACTCCTAGGACCCCTTCTCGTGTTACAGGCG				
S15	TGGAGAACATCACATCAGGACTCCTAGGACCCCTTCTCGTGTTACAGGCG				

	360	370	380	390	400
S0				CGCAGAGTCTAGACTC	
S6					
S8	GGGTTTTTCTTGTTGACAAGAATCCTCACAATACCGCAGAGTCTAGACTC				
S12	GGGTTTTTCTTGTTGACAAGAATCCTCACAATACCGCAGAGTCTAGACTC				
S15	GGGTTTTTNTTGTGACAAGAATCCTCACAATACCGCAGAGTCTAGACTC				

	410	420	430	440	450
S0	GTGGTGGACTTCTCTCAATTTTCGAGGGGGGACTACCGTGTGTCTTGGCC				
S6					
S8	GTGGTGGACTTCTCTCAATTTTCGAGGGGGGACTACCGTGTGTCTTGGCC				
S12	GTGGTGGACTTCTCTCAATTTTCGAGGGGGGACTACCGTGTGTCTTGGCC				
S15	GTGGTGGACTTCTCTCAATTTTCGAGGGGGGACTACCGTGTGTCTTGGCC				

	460	470	480	490	500
S0	AAAATTGCGAGTCCCCAACCTCCAATCACTCACCAACCTCCTGTCTCTCCA				
S6		TTACTCACCNACCTCCTGTCTCTCCA			
S8	AAAATTGCGAGTCCCCAACCTCCAATCACTCACCAACCTCCTGTCTCTCCA				
S12	AAAATTGCGAGTCCCCAACCTCCAATCACTCACCAACCTCCTGTCTCTCCA				
S15	AAAATTGCGAGTCCCCAACCTCCAATCACTCACCAACCTCCTGTCTCTCCA				

	510	520	530	540	550
S0	ACTTGTCTGCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCATCTTCTCT				
S6	ACTTGTCTGCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCATCTTCTCT				
S8	ACTTGTCTGCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCATCTTCTCT				
S12	ACTTGTCTGCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCATCTTCTCT				
S15	ACTTGTCTGCTGGTTATCGCTGGATGTGTCTGCGGCGTTTTATCATCTTCTCT				

	560	570	580	590	600
S0	CTTCATCCTGCTGCTATGCCTCATCTTCTTGTGGTTCTTCTGGACTGTC				
S6	CTTCATCCTGCTGCTATGCCTCATCTTCTTGTGGTTCTTCTGGACTGTC				
S8	CTTCATCCTGCTGCTATGCCTCATCTTCTTGTGGTTCTTCTGGACTGTC				
S12	CTTCATCCTGCTGCTATGCCTCATCTTCTTGTGGTTCTTCTGGACTGTC				
S15	CTTCATCCTGCTGCTATGCCTCATCTTCTTGTGGTTCTTCTGGACTGTC				

	610	620	630	640	650
S0	AAGGTATGTTGCCCCGTTTGTCTCTAATTCCAGGATCCTCAACCACCAGC				
S6	AAGGTATGTTGCCCCGTTTGTCTCTAATTCCAGGATCCTCAACCACCAGC				
S8	AAGGTATGTTGCCCCGTTTGTCTCTAATTCCAGGATCCTCAACCACCAGC				
S12	AAGGTATGTTGCCCCGTTTGTCTCTAATTCCAGGATCCTCAACCACCAGC				
S15	AAGGTATGTTGCCCCGTTTGTCTCTAATTCCAGGATCCTCAACCACCAGC				

Figure 7 (continued)

	660	670	680	690	700
S0	ACGGGACCATGCCGAACCTGCACGACTCCTGCTCAAGGAACCTCTACGGT				
S6	AGGGGACCATGCCGAACCTGCACGACTCCTGCTCAAGGAACCTCTACGGT				
S8	AGGGGACCATGCCGAACCTGCACGACTCCTGCTCAAGGAACCTCTACGGT				
S12	AGGGGACCATGCCGAACCTGCACGACTCCTGCTCAAGGAACCTCTACGGT				
S15	AGGGGACCATGCCGAACCTGCACGACTCCTGCTCAAGGAACCTCTACGGT				
	710	720	730	740	750
S0	TCCCTCATGTTGCTGTACCAAACCTTCGGACGGAAATTGCACCTGTATTTC				
S6	TCCCTCATGTTGCTGTACCAAACCTTCGGACGGAAATTGCACCTGTATTTC				
S8	TCCCTCATGTTGCTGTACCAAACCTTCGGACGGAAATTGCACCTGTATTTC				
S12	TCCCTCATGTTGCTGTACCAAACCTTCGGACGGAAATTGCACCTGTATTTC				
S15	TCCCTCATGTTGCTGTACCAAACCTTCGGACGGAAATTGCACCTGTATTTC				
	760	770	780	790	800
S0	CCATCCCATCATCCTGGGCTTTTCGGAAAAATTCCTATGGGAGTGGGCCTCA				
S6	CCATCCCATCATCCTGGGCTTTTCGGAAAAATTCCTATGGGAGTGGGCCTCA				
S8	CCATCCCATCATCCTGGGCTTTTCGGAAAAATTCCTATGGGAGTGGGCCTCA				
S12	CCATCCCATCATCCTGGGCTTTTCGGAAAAATTCCTATGGGAGTGGGCCTCA				
S15	CCATCCCATCATCCTGGGCTTTTCGGAAAAATTCCTATGGGAGTGGGCCTCA				
	810	820	830	840	850
S0	GCCCGTTTCTCCTGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGGTTCGT				
S6	GCCCGTTTCTCATGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGGTTCGT				
S8	GCCCGTTTCTCATGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGGTTCGT				
S12	GCCCGTTTCTCATGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGGTTCGT				
S15	GCCCGTTTCTCATGGCTCAGTTTACTAGTGCCATTTGTTTCAGTGGTTCGT				
	860	870	880	890	900
S0	AGGGCTTTCCCCCACTGTCTGGCTTTTGGTTATGTGGATGATGTGGTATT				
S6	AGGGCTTTCCCCCACTGTCTGGCTTTTGGTTATGTGGATGATGTGGTATT				
S8	AGGGCTTTCCCCCACTGTCTGGCTTTTGGTTATGTGGATGATGTGGTATT				
S12	AGGGCTTTCCCCCACTGTCTGGCTTTTGGTTATGTGGATGATGTGGTATT				
S15	AGGGCTTTCCCCCACTGTCTGGCTTTTGGTTATGTGGATGATGTGGTATT				
	910	920	930	940	950
S0	GGGGGCCAAGTCTGTATCGCATCTTGAGTCCCTTTTTACCGCTGNTACCA				
S6	GGGGGCCAAGTCTGTATCGCATCTTGAGTCCCTTTTTACCGCTGTTACCA				
S8	GGGGGCCAAGTCTGTATCGCATCTTGAGTCCCTTTTTACCGCTGTTACCA				
S12	GGGGGCCAAGTCTGTATCGCATCTTGAGTCCCTTTTTACCGCTGTTACCA				
S15	GGGGGCCAAGTCTGTATCGCATCTTGAGTCCCTTTTTACCGCTGTTACCA				
	960	970	980	990	1000
S0	ATTTTCTTTTGTCTTTGGGTATACATTTAAACCCTAACAAAACAAAAGA				
S6	ATTTTCTTTTGTCTTTGGGTATACATTTAAATCCTAACAAAACAAAAGA				
S8	ATTTTCTTTTGTCTTTGGGTATACATTTAAATCCTAACAAAACAAAAGA				
S12	ATTTTCTTTTGTCTTTGGGTATACATTTAAATCCTAACAAAACAAAAGA				
S15	ATTTTCTTTTGTCTTTGGGTATACATTTAAATCCTAACAAAACAAAAGA				
	1010	1020	1030	1040	1050

Figure 7 (continued)

S0 TGGGGTTACTCCCTACATTTTATGGGCTATGTCATTGGAT  
S6 TGGGGTTACTCCCTACATTTTATGGGCTATGTCATTGGATGTCATGGGTC  
S8 TGGGGTTACTCCCTACATTTTATGGGCTATGTCATTGGATGTCATGGGTC  
S12 TGGGGTTACTCCCTACATTTTATGGGCTATGTCATTGGATGTCATGGGTC  
S15 TGGGGTTACTCCCTACA

	1060	1070	1080	1090	1100
S0					
S6	CTTGCCACAAGAACACATCAGACAAAAAATCAAAGAATGTTTTAGAAAAC				
S8	CTTGCCACAAGAACACATCAGACAAAAAATCA				
S12	CTTGCCACAAGAACACATCAGACAAAAAATCAAAGAATGTTTTAGAAAAC				
S15					

## Figure 7 (continued)

	260	270	280	290	300	
S0	SGHTTNFASKSTSCCLHQSPVRKAAYPAVSTFERHSSSGHAVELNNLPPNS					[SEQ ID NO:25]
S6						[SEQ ID NO:26]
S8	CPFCLHQSPVRKAAYPAVSTFERHSSSGHAVELNNLPPNS					[SEQ ID NO:27]
S12	SGHITNSASKSTSCCLHQSPVRKAAYPAVSTFERHSSSGHAVELNNLPPNS					[SEQ ID NO:28]
S15	TNFASKSTSCCLHQSPVRKAAYPAVSTFERHSSSGHAVELNNLPPNS					[SEQ ID NO:29]

	310	320	330	340	350	
S0	ARSQSERPVFPCWWLQFRNSKPCSDYCLSLIVNLLEDWGPCAEGEHHR					
S6						
S8	ARSQSERPVFPCWWLQFRNSKPCSDYCLSLIVNLLEDWGPCAEGEHHR					
S12	ARSQSERPVFPCWWLQFRNSKPCSDYCLSLIVNLLEDWGPCAEGEHHR					
S15	ARSQSERPVFPCWWLQFRNSKPCSDYCLSLIVNLLEDWGPCAEGEHHR					

	360	370	380	390	400	
S0	TPRTPSRVTGGVFLVDKNPHNTAESRLVVDIFSQFSRGDYRVSWPKFAVPN					
S6						
S8	TPRTPSRVTGGVFLVDKNPHNTAESRLVVDIFSQFSRGDYRVSWPKFAVPN					
S12	TPRTPSRVTGGVFLVDKNPHNTAESRLVVDIFSQFSRGDYRVSWPKFAVPN					
S15	TPRTPSRVTGGVFXVDKNPHNTAESRLVVDIFSQFSRGDYRVSWPKFAVPN					

	410	420	430	440	450	
S0	LQSLTNLLSSNLSWLSLDVSAAFYHLPLHPAAMPHELLVGSSGLSRYVARL					
S6	SNLSWLSLDVSAAFYHLPLHPAAMPHELLVGSSGLSRYVARL					
S8	LQSLTNLLSSNLSWLSLDVSAAFYHLPLHPAAMPHELLVGSSGLSRYVARL					
S12	LQSLTNLLSSNLSWLSLDVSAAFYHLPLHPAAMPHELLVGSSGLSRYVARL					
S15	LQSLTNLLSSNLSWLSLDVSAAFYHLPLHPAAMPHELLVGSTGLSRYVARL					

	460	470	480	490	500	
S0	SSNSRILNHQHGTMPLNLDSCSRNLYGSLMLLYQTFGRKLHLYSHPIILG					
S6	SSNSRILNHQQGTMPNLDSCSRNLYGSLMLLYQTFGRKLHLYSHPIILG					
S8	SSNSRILNHQQGTMPNLDSCSRNLYGSLMLLYQTFGRKLHLYSHPIILG					
S12	SSNSRILNHQQGTMPNLDSCSRNLYGSLMLLYQTFGRKLHLYSHPIILG					
S15	SSNSRILNHQQGTMPNLDSCSRNLYGSLMLLYQTFGRKLHLYSHPIILG					

	510	520	530	540	550	
S0	FRKIPMGVGLSPFLMAQFTSAICSVVRRAPPHCLAFGYVDDVVLGAKSVS					
S6	FRKIPMGVGLSPFLMAQFTSAICSVVRRAPPHCLAFGYVDDVVLGAKSVS					
S8	FRKIPMGVGLSPFLMAQFTSAICSVVRRAPPHCLAFGYVDDVVLGAKSVS					
S12	FRKIPMGVGLSPFLMAQFTSAICSVVRRAPPHCLAFGYVDDVVLGAKSVS					
S15	FRKIPMGVGLSPFLMAQFTSAICSVVRRAPPHCLAFGYVDDVVLGAKSVS					

	560	570	580	590	600	
S0	HLESLEFTAVTNFLLSLGIHLNPNKTKRWGYSLHFMGYVIGCHGSLPQEH					
S6	HLESLEFTAVTNFLLSLGIHLNPNKTKRWGYSLHFMGYVIG					
S8	HLESLEFTAVTNFLLSLGIHLNPNKTKRWGYSLHFMGYVIGCHGSLPQEH					
S12	HLESLEFTAVTNFLLSLGIHLNPNKTKRWGYSLHFMGYVIG					
S15	HLESLEFTAVTNFLLSLGXHLNPNKTKRWGYS					

Figure 8

	10	20	30	40	50	
S0						[SEQ ID NO:30]
S6						[SEQ ID NO:31]
S8						[SEQ ID NO:32]
S12	LGSPQAQGILQTLPANPPPASTNRQSGRQPTPLSPPLRDTHPQAMQWNST					[SEQ ID NO:33]
S15		PPFASTNRQSGRQPTPLSPPLRDTHPQAMQWNST				[SEQ ID NO:34]

	60	70	80	90	100	
S0						
S6						
S8						
S12	TFHQTLQDPRVKGLYFPAGGSSSGTVNPVPTTASHSSSIFSRIGVPALNM					
S15	TFHQTLQDPRVKGLYFPAGGSSSGTVNPVPTTASHSSSIFSRIGVPALNM					

	110	120	130	140	150	
S0			QSLDSWWTSLNFRGGTTVCLGQ			
S6						
S8						
S12	ENITSGLLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFRGGTTVCLGQ					
S15	ENITSGLLGPLLVLQAGFFLLTRILTIPQSLDSWWTSLNFRGGTTVCLGQ					

	160	170	180	190	200	
S0	NSQSPTSNSHPTSCPPTCPGYRWMCLRRFIIIFLFIILLCLIFLLVLLDCQ					
S6		PPTCPGYRWMCLRRFIIIFLFIILLCLIFLLVLLDCQ				
S8		PTCPGYRWMCLRRFIIIFLFIILLCLIFLLVLLDCQ				
S12	NSQSPTSNSHPTSCPPTCPGYRWMCLRRFIIIFLFIILLCLIFLLVLLDCQ					
S15	NSQSPTSNSHPTSCPPTCPGYRWMCLRRFIIIFLFIILLCLIFLLVLLDCQ					

	210	220	230	240	250	
S0	GMLPVCPLIPGSSTTSTGPCRTCTTPAQGTSTVPSCCCTKPSDGNCTCIP					
S6	GMLPVCPLIPGSSTTSTGPCRTCTTPAQGTSTVPSCCCTKPSDGNCTCIP					
S8	GMLPVCPLIPGSSTTSTGPCRTCTTPAQGTSTVPSCCCTKPSDGNCTCIP					
S12	GMLPVCPLIPGSSTTSTGPCRTCTTPAQGTSTVPSCCCTKPSDGNCTCIP					
S15	GMLPVCPLIPGSSTTSTGPCRTCTTPAQGTSTVPSCCCTKPSDGNCTCIP					

	260	270	280	290	300	
S0	IPSSWAFGKFLWEWASARFSWLSLLVPFVQWVGLSPTVWLLVIWMMWYW					
S6	IPSSWAFGKFLWEWASARFSWLSLLVPFVQWVGLSPTVWLLVMWMMWYW					
S8	IPSSWAFGKFLWEWASARFSWLSLLVPFVQWVGLSPTVWLLVMWMMWYW					
S12	IPSSWAFGKFLWEWASARFSWLSLLVPFVQWVGLSPTVWLLVMWMMWYW					
S15	IPSSWAFGKFLWEWASARFSWLSLLVPFVQWVGLSPTVWLLVMWMMWYW					

	310	320	
S0	GPSLYRILSPFLPLXPIFFCLWVYI		
S6	GPSLYRILSPFLPLLPIFFCLWVYI		
S8	GPSLYRILSPFLPLLPIFFCLWVYI		
S12	GPSLYRILSPFLPLLPIFFCLWVYI		
S15	GPSLYRILSPFLPLLPIFFCLWVXI		

Figure 9

10 20 30 40 50 60 70 80 90 100  
 TACTACAAACCTTGGCAGCAAAATCCGCCCTCCTGTCTTACCAATCGCCAGTCAGGAAGGCAGCCTACCCCTCTGACTCCACCTTTTGAGAAACACTCATCC  
 110 120 130 140 150 160 170 180 190 200  
 TCAGGCCATGCA GTGGAACTCCACAAACTTCCACCGAACTCTACAAGATCCAGAGTGAAGGCCCTGTATCTCCCTGTGTGGCTCCAGTTTCAGGAACA  
 210 220 230 240 250 260 270 280 290 300  
 GTAAACCTGTTCGGACTACTGTCTCTCACACATCGTCAATCTTATCGAGGATGGGGACCCCTGCAC TGAACATGGAGAACATCATCAGGATTCCTTAG  
 310 320 330 340 350 360 370 380 390 400  
 GACCCCTGTCTGTGTACAGGCGGGGTTTTTCTTGTGACAAGAAATCCTCACAAATACCGCAGAGTCTAGACTCGTGGTGGACTTCTCTCAATTTTCTTAGG  
 410 420 430 440 450 460 470 480 490 500  
 GGGGACCAACCGTGTGCCCTTGGCCAAATTCGCAGTCCCAACCTCCAAATCACTCACCAACCTCCTGTCTCCTCAACTTGTCTCTGGTTATCGCTGGATGTGT  
 510 520 530 540 550 560 570 580 590 600  
 CTGCGGCGTTTTATCATATTCCTCTTCATCCTGTCTGTATGCTCATCTCTTGTGGTTCTTCTGGACTATCAAGGTATGTGTGCCGTTTGCCCTCTTAA  
 610 620 630 640 650 660 670 680 690 700  
 TTCCAGGATCCTCAACCAACAGCAGCGGACCATGTCAGAACCTGTCAGACTCCTGCTCAAGGAACCTCTWTGTATCCCTCATGTGTGCTGTACCAAAACCTTWC  
 710 720 730 740 750 760 770 780 790 800  
 GEMCGSAAATGACACCTGTATTCCTCCATCCCATCATCTCTGGGCTTTCGGAATAATTCCTATGGGAGTGGGCCCTCAGCCCGTTCTCTCTGACTCAGTTTACTA  
 810 820 830 840 850 860 870 880 890 900  
 GTGCCAATTTGTTTCA GTGGTTCGTAGGGCTTTCCTCCACACTGTTTGGCTTTCAGTTATATGGATGATGTGGTATTTGGGGCCAGGTCTGTGTACAGCATCGTGA  
 910 920 930 940 950 960 970 980 990 1000  
 GGCCCTTTTACCGCTGTACCAATTTTCTTTTGTCTCTGGGTATACATTTAAACCCGGACAAAACAAAAGATGGGGTTACTCTTTTACATTTTCATGGGC  
 1010 1020 1030  
 TATGTCAATGGGATGTTATGGGTCAATTGCCAC

Figure 10

10	20	30	40	50	60	70	80	90	100
TTNLASKSACLYQSPVRKAAYPSDSTFEKHSSSGHAVELHKLPPNSTRSQSERPVSPCWLQFRNSKPCSDYCLSHIVNLIEDWGPCTEHGEHHRIPR									
110	120	130	140	150	160	170	180	190	200
TPARVTGGVFLVDKNPHNTAESRLVDFSQFSRGDHRVPWPKFAVNPQLQSLTNLLSSNLISLIDVSAAFYHIPHHPAAMPHELLVGSSGLSRYVARLPNS									
210	220	230	240	250	260	270	280	290	300
SRIILNHQGTMONLHDSCSRNLV/FVSLMLLYQTF/TGRKLHLYSHPIILGFRKIPMGVGLSPFLLTQFTSAICSVVRRAPPHCLAFSYMDVVVLGARSVQ									
310	320	330	340						
HREALFTAVTNFLLSLGIHLTPDKTKRWGYSLSLHFMGYVIGCYGSLP									

Figure 11



10	20	-30	40	50	60	70	80	90	100
LQTLPANPPPA	STNRQSGRQPTPLTPPLRNTHPQAMQWNSTNFHRTLQDPRVKGLYLPAGSSSGTVNPFVTTVSH	TSSILSRIGDPALNMENITSGFLG							
110	120	130	140	150	160	170	180	190	200
PLLVLAQGFELL	TRILTIPOSILDSWWTSINFLGGTTVCLGQNSQSPTSNSHSP	TCPGYRWMCLRRFIIIFLFI	LLCLIFLLVLLDDYQGM	LPVCP	LI				
210	220	230	240	250	260	270	280	290	300
PGSSTTSTG	PCRTCTTTPAQGTSM/LYPSCCCTKPS/TAANCTCIP	IPSSWAFGKFLN	EWASARFS*LSLLVPFVQNFVGLSPTV	WLSVIWNWYWGPGILYS					
310									
IVRPFLLP	LLPIFFCLMVYI								

Figure 12

10 20 30 40 50 60 70 80 90 100  
 TGGTCACAGTGCCCAACAGTTCCCTCCTCCCTCCACCAATCGGCAGTCAGGGAGGCAGCCTACTCCCATCTCTCCACCTCTAAGAGACAGTCATCCTCA  
 110 120 130 140 150 160 170 180 190 200  
 GGCCATGGTGGCTCAGCCCTGCTGGTGGCTCCAGTTCAGGAACACTCAACCCCTGTTCCCAATATTGGCTCTCACATCTCGTCAATCTCCTTGAGGACTGGG  
 210 220 230 240 250 260 270 280 290 300  
 GACCCTGCGCCGAACATGGAGAACATCACAATCAGGATTCCTAGGACCCCTGCTCGTGTACAGGCGGGGTTTTCTTGTGTGACAAAGAATCCTCACAAATAC  
 310 320 330 340 350 360 370 380 390 400  
 CGCAGAGTCTAGACTCGTGGTGGACTTCTCTCAGTTTTCTAGGGGGATCACCCGTTGTCTTTGGCCAAAATTTCGCAGTCCCCAACCTCCAATCACCTCACC  
 410 420 430 440 450 460 470 480 490 500  
 AACCTCCTGTCTCCTCAATTGACCTGGTTATCGCTGGATATGTCTGCGGCGTTTTTATCATATTCCTCTTCATCTCTGCCGTATGCCCTCATCTTCTTATIG  
 510 520 530 540 550 560 570 580 590 600  
 GTTCTTCTGGATTATCAAGGTATGTTGCCCGTTTGTCTCTTAATTCAGGATCCACAACAACAGTGGCGGACCCCTGCAAAACCTGCACGACTCCTGCTC  
 610 620 630 640 650 660 670 680 690 700  
 AAGGCAACTCTATGTTTCCCTCATGTTGCTGTACAAAACCTACGGATGGAAATTGCACCTGTATTCCCATCCCATCATCTTGGGCTTTCGCAAAATACCT  
 710 720 730 740 750 760 770 780 790 800  
 ATGGGAGTGGGCCCTCAGTCCGTTTCTTGGCTCAGTTTACTAGTGCCATTGTTTCAGTGATTCGTAGGGCTTTCGCCACTGTTTGGCTTTCAGCTATA  
 810 820 830 840 850 860 870 880  
 TTGATGATGTGGTACTGGGGGCCAAGTCTGCACAACATCTTGAGTCCCTTTATACCGCTGTTACCAATTTCTTTTGTCTTTGGGTAT

Figure 13

10	20	30	40	50	60	70	80	90	100
GHSANSSSCLHQSAVREAA	YSHLSTSKRQSSGHGGSACW	LQFRNTQPCSQYCLSHLVNLL	EDWGPCAEHGEHHRIPRTPAR	VTGGVFLVDKNPHNT					
110	120	130	140	150	160	170	180	190	200
AESRLVVD	FSQFSGITRVSWPKFAV	PNLQSLTNLLSSNLTWLSL	DMSAAFYHIDLP	PAAMP	PHLLIGSSGLSRYV	ARLSSNSRIHNNQCG	TLOMLHDS	SCS	
210	220	230	240	250	260	270	280	290	
RQLYVSLMLLYKTYG	WKLHLYSHPIILGFRKIP	MGVGLSPFLLAQFTSAICS	VIRRAFP	CHCLAFSYID	DDVVLGAKSAQH	LES	LYTAV	TN	FLLSLG

Figure 14

10	20	30	40	50	60	70	80	90	100
VTVPTVPPASTNRQSGRQPTPI	SPPLRDSHPQAMVAQ	PAGSSSGTLN	VPVNIASHISSISLRTGDP	PAPNMENITSGFLGPLLV	LQAGFFLL	TRIL	TIP		
110	120	130	140	150	160	170	180	190	200
QSLDSWWTSLSLFLGGSPVCLG	QNSQPTSNHSP	TSCPPI*PGYRWICLRR	FIIFLFIPLCLIFL	VLVDYQGM	LPVCPLIPG	STTSAGPCKTCT	TPAQ		
210	220	230	240	250	260	270	280	290	
GNSMFPSCCCTKPTDGNCTC	IPIPSSWAF	AKYLMW	EWASVRF	SWLSLLVPFVQ*FVGLSPTVWLSAILMMWYWG	PSLHNILSPFIP	LLPIFFCL	WV		

Figure 15

10 20 30 40 50  
TCCTGTCCTCCAATTTGTCCTGGTTATCGCTGGATGTGTCTGCGGCGTTT

60 70 80 90 100  
TATGATATTCTCTTCATCCTGCTGCTATGCCTCATCTTCTTATTGGTTC

110 120 130 140 150  
TTCTGGATTATCAAGGTATGTTGCCCCGTCTGTCCTCTAATTCCAGGATCA

160 170 180 190 200  
ACAACAACCAGTACGGGACCATGCAAAACCAAAACCTGCACGACTCCTGC

210 220 230 240 250  
TCAAGGCAACTCTATGTTTCCCTCATGTTGCTGTACAAAACCTACGGATG

260 270 280 290 300  
GAAATTGCACCTGTATTCCCATCCCATCGTCCTGGGCTTTCGCAAAATTC

310 320 330 340 350  
CTATGGGAGTGGGCCTCAGTCCGTTTCTCTTGGCTCAGTTTACTAGTGCC

360 370 380 390 400  
ATTTGTTCAGTGGTTTCGTAGGGCTTTCCTCCCACTGTTTGGCTTTCAGCTA

410 420 430 440 450  
TATGGATGATGTGGTATTGGGGGCCAAGTCTGTACAGCATCGTGAGGCCC

460 470 480 490 500  
TTTATACAGCTGTTACCAATTTTCTTTTGTCTCTGGGTATACATTTAAAC

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560 570 580 590  
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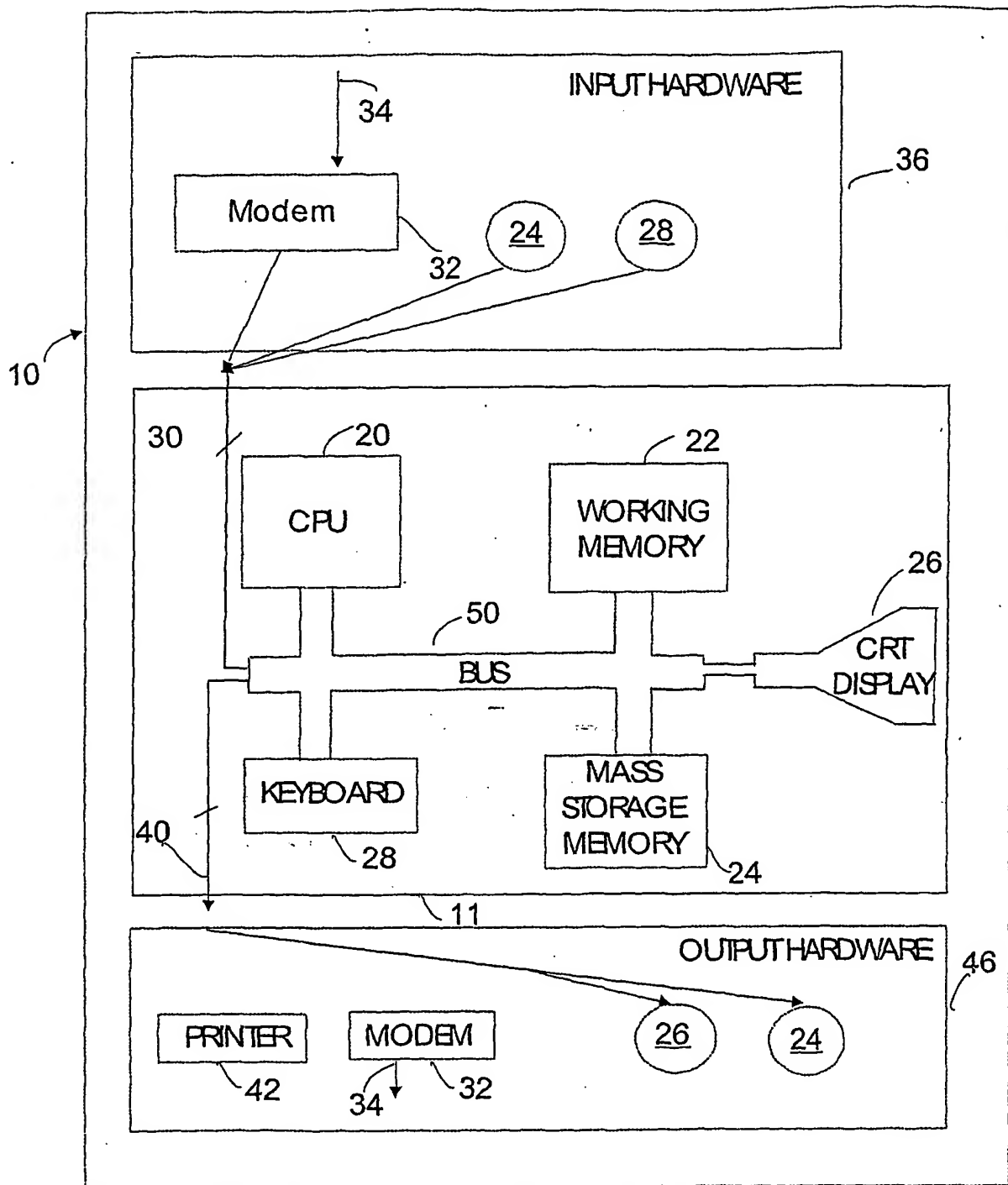
**Figure 16**

10	20	30	40	50
SNLSWLSLDVSAAFYDIPLHPAAMPHELLIGSSGLSRYVARLSSNSRINNN				
60	70	80	90	100
QYGTMQNQNLHDSCSRQLYVSLMLLYKTYGWKLHLYSHPIVLGFRKIPMG				
110	120	130	140	150
VGLSPFLLAQFTSAICSVVRRAFPCLAFSYMDDVVLGAKSVQHREALYT				
160	170	180		
AVTNFLLSLGIHLNPNKTKRWGYSLNFMGYIIGSWG				

**Figure 17**

10	20	30	40	50
SCPPICPGYRWMCLRRFMIFLLCLIFLLVLLDYQGMLPVCPLIPGS				
60	70	80	90	100
TTTSTGPCKTKTCTTPAQGNSMFPSCCCTKPTDGNCTCIPSSWAFKF				
110	120	130	140	150
LWEWASVRFSWLSLLVPFVQWFVGLSPTVWLSAIWMMWYGPSLYSIVRP				
160				
FIQLLPPIFFCLWVYI				

**Figure 18**

**Figure 19**



```

      10      20      30      40      50
AATCCTCACAATACCGCAGAGTCTAGACTTCGTGGTGACTTCTCTCAATT

      60      70      80      90     100
TTCTAGGGGACCACCCGTGTGTCTTGGCCAAAATTTCGCAGTCCCCAACCT

     110     120     130     140     150
CCAATCACTCACCAACCTCTTGTCTCTCAATTTGTCCTGGTTATCGCTGG

     160     170     180     190     200
ATGTGTCTGCGGCGTTTTATCATATCCCTCTTCATCCTGCTGCTATGCCT

     210     220     230     240     250
CATCTTCTTATTGGTTCTTCTGGATTATCAAGGTATGTTGCCCGTTTGTC

     260     270     280     290     300
CTCTAATTCCAGGATCCACAACAACAGTACGGGACCCTGCAAAACCTGC

     310     320     330     340     350
ACGACTCCTGCTCAAGGCAACTCTATGTTTCCCTCATGTTGCTGTACAAA

     360     370     380     390     400
ACCTACGGATGGAAATTGCACMTGTATTCCCATCCCATCATCTTGGGCTT

     410     420     430     440     450
TCGCAAAATACCTATGGGAGTGGGCCTCAGTCCGTTTCTCTTGGTTCAGT

     460     470     480     490     500
TTACTAGTGCCATTTGTTTCAGTGGTTCGTAGGGCTTTCCCCCACTGTTTG

     510     520     530     540     550
GCTTTCAGCTATATGGATGATATTGTACTGGGGGCCAAGTCTGTACAACA

     560     570     580     590     600
TCTTGAGTCCCTTTATACCGCTGTTACCAATTTTCTTTTGTCTTTGGGTA

     610     620     630     640     650
TACATTTAACCCCTAACAAAACAAAGAGATGGGGTTATTCCCTGAATTC

     660
ATGGGTTATGTAATTGGAA

```

**Figure 20**

10 20 30 40 50  
SNLSWLSLDVSAAFYHIPLHPAAMPHLLIGSSGLSRYVARLSSNSRIHNN  
60 70 80 90 100  
QYGTQLQNLHDSCSRQLYVSLMLLYKTYGWLHXYSHPIILGFRKIPMGVG  
110 120 130 140 150  
LSPFLLVQFTSAICSVVRRAFPCLAFSYMDDIVLGAKSVQHLESlyTAV  
160 170 180  
TNFLLSLGIHLTPNKTKRWGYSLNFMGYVIG

**Figure 21**

10 20 30 40 50  
PICPGYRWMCLRRFIISLFILLCLIFLLVLLDYQGMLPVCPLIPGSTTT  
60 70 80 90 100  
STGPCKTCTTPAQGNSMFPSCCCTKPTDGNCTCIPSSWAFAYLWEWA  
110 120 130 140 150  
SVRFSWFSLVPFVQWFVGLSPTVWL\_SAIWMILYWGPSLYNILSPFIPLL  
160  
PIFFCLWVYI

**Figure 22**

10 20 30 40 50  
TCCAATTTGTCCTGGGTATCGCTGGATGTGTCTGCGGCGTTTTATCATAT

60 70 80 90 100  
TCCTCTTCATCCTGCTGCTATGCCTCATCTTCTTGTTGGTTCTTCTGGAC

110 120 130 140 150  
TATCAAGGTATGTTGCCCCTTGTCTCTACTTCCAGGAACATCAACTAC

160 170 180 190 200  
CAGCACGGGACCATGCAAGACCTGCACGACTCCTGCTCAAGGAACCTCTA

210 220 230 240 250  
TGTTTCCCTCTTGTTGCTGTACAAAACCTTCGGACGGAAATTGCACTTGT

260 270 280 290 300  
ATTCCCATCCCATCGTCTTGGGCTTTCGCAAGATTCCCTATGGGAGTGGGC

310 320 330 340 350  
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360 370 380 390 400  
TCGTAGGGCTTTCCCCCACTGTTTGGCTTTCAGTTATATTGATGATGTGG

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460 470 480 490 500  
ACCAATTTTCTTATGTCTTTGGGTATACATTTAAACCCTAAGAAAACCAA

510 520 530 540 550  
ACGTTGGGGCTACTCCCTTAACTTCATGGGATATGTAATTGGAAGTTGGG

GTAC

**Figure 23**

10	20	30	40	50
SNLSWVSLDVSAAFYHIPLHPAAMPHELLVGSSGLSRYVARLSSTSRNINY				
60	70	80	90	100
QHGTMQDLHDSCSRNLYVSLLLLYKTFGRKLHLYSHPIVLGFRKIPMGVG				
110	120	130	140	150
LSPFLLAQFTSAICSVVRRAFPCLAFSYIDDVVLGAKSVQHLESLETSI				
160	170	180		
TNFLMSLGIHLNPKKTKRWGYSLNFMGYVIGSWG				

**Figure 24**

10 20 30 40 50  
PICPGYRWMCLRRFIIIFLFILLLLCLIFLLVLLDYQGMLPVCPLLPGTSTT  
60 70 80 90 100  
STGPCKTCTTPAQGTSMFPSCCCTKPSDGNCTCIPSSWAFARFLWEWA  
110 120 130 140 150  
SVRFSWLXLLVPFVQWFVGLSPTVWLSVILMMWYGPSLYNILNPFLPLL  
160  
PIFLCLWVYI

**Figure 25**

10	20	30	40	50
CAGCAAATCCGCCTCCTGCCTCTACCAATCGCCAGTCAGGAAGGCAGCCT				
60	70	80	90	100
ACCCCTCTGTCTCCACCTTTTGRGAAACACTCATCCTCAGGCCATGCAGTG				
110	120	130	140	150
GAACTCCACAACCTTCCACCAAACCTCTGCWAGATCCCAGAGTGAGAGGCC				
160	170	180	190	200
TGTATTTCCCTGCTGGTGGCTCCAGTTCAGGAACAGTAAACCCTGTTCCG				
210	220	230	240	250
ACTTCTGTCTCTCACACATCGTCAATCTTCTCGAGGATTGGGGWCCCTGC				
260	270	280	290	300
GCTGAACATGGAGAACATCACATCAGGATTCTAGGACCCCTGCTCGTGT				
310	320	330	340	350
TACAGGCGGGGTTTTTCTTGTTGACAAGAATCCTCACAATACCGCAGAGT				
360	370	380	390	400
CTAGACTCGTGGTGGACTTCTCTCAATTTTCTAGGGGGAACTACCGTGTG				
410	420	430	440	450
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460	470	480	490	500
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ATCTTCCTCTTCATCCTGCTGCTATGCCTCATCTTCTTGTTGGTTCTTCT				
560	570	580	590	600
GGACTATCAAGGTATGTTGCCCCGTTTGTCCTCTARTTCCAGGATCTTCAA				
610	620	630	640	650
CCACCAGCACGGGACCATGCAGAACCTGCACGACTCCTGCTCAAGGAAMC				
660	670	680	690	700
TCTATGAATCCCTCCTGTTGCTGTACCAAACCTTCGGACGGAAATTGCAC				
710	720	730	740	750
CTGTATTCCCATCCCATCATCCTGGGCTTTCGGAAAATTCCCTATGGGAGT				
760	770	780	790	800
GGGCCTCAGCCCGTTTCTCCTGRCTCAGTTTACTAGTGCCATTTGTTTACG				
810	820	830	840	850
TGGTTCGTAGGGCTTTCCCCCACTGTTTGGCTTTCAGTTATATGGATGAT				
860	870	880	890	900
GTGGTATTGGGGGCCAAGTCTGTAYMGCATCTTRAGTCCCTTTTACCGC				
910	920	930	940	950
TGTTACCAATTTTCTTTTGTCTYTGGGTATACATTTAAACCCTMACAAAA				
960	970	980	990	1000
CAAAAAGATGGGGTTACTCTTTACATTTTCATGGGCTATGTCATTGGATGT				
1010	1020	1030	1040	
TATGGGTTCATTGCCACAAGATCACATCAGACAGAAAATCAAAGAA				

Figure 26

10	20	30	40	50
SKSASCLYQSPVRKAAYPSVSTFXKHSSSGHAVELHNLPPNSARSQSERP				
60	70	80	90	100
VFPCWWLQFRNSKPCSDFLSHIVNLLEDWGPCAEGEHHIRIPRTPARV				
110	120	130	140	150
TGGVFLVDKNPHNTAESRLVVDIFSQFSRGNYRVSWPKFAVPNLQSLTNLL				
160	170	180	190	200
SSNLXWLSLDVSAAFYHLPLHPAAMPHLIVGSSGLSRYVARLSSXSRIFN				
210	220	230	240	250
HQHGTMQNLHDSCSRXLYESLLLLLYQTFGRKLHLYSHPIILGFRKIPMGV				
260	270	280	290	300
GLSPFLLXQFTSAICSVVRRAPPHCLAFSYMDDVVLGAKSVXHLXSLFTA				
310	320	330	340	
VTNFLLSLGIHLNPXKTKRWGYSLHFMGYVIGCYGSLPQDHIRQKIKE				

**Figure 27**



10 20 30 40 50  
ANPPPASTNRQSGRQPTPLSPPLXNTHPQAMQWNSTTFHQTLXDPRVRGL

60 70 80 90 100  
YFPAGGSSSGTVNVPVPTSVSHTSSIFSRIGXPALNMENITSGFLGPLLVL

110 120 130 140 150  
QAGFFLLTRILTIPQSLDSWWTSLNFLGGTTVCLGQNSQFPTSNHSPTSC

160 170 180 190 200  
PPTXPGYRWMXLRRFIIFLFILLCLIFLLVLLDYQGMLPVCPLXPGSST

210 220 230 240 250  
TSTGPCRTCTTPAQGXSMNPSCCCTKPSDGNCTCIPSSWAFGKFLWEW

260 270 280 290 300  
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**Figure 28**

SEQUENCE LISTING

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Southern Health (for all States except the US)  
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Locarnini, Stephen (US only)  
Ayres, Anna (US only)  
Colledge, Danielle (US only)  
Sasadeusz, Joseph (US only)  
Tillmann, Hans (US only)  
Angus, Peter (US only)  
Sievert, William (US only)

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Asp Lys Asn Pro His Asn Thr Xaa Glu Ser Xaa Leu Xaa Val Asp Phe  
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Ser Gln Phe Ser Arg Gly Xaa Xaa Xaa Val Ser Trp Pro Lys Phe Ala  
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<223> M = amino acid 204

<220>  
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<222> (133)..(133)  
<223> X = V or L or M

<220>  
<221> MISC\_FEATURE  
<222> (138)..(138)  
<223> X = K or R

<220>  
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<222> (139)..(139)  
<223> X = S or T



<220>  
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<222> (140)..(140)  
<223> X = V or G

<220>  
<221> MISC\_FEATURE  
<222> (141)..(141)  
<223> X = Q or E

<220>  
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<222> (143)..(143)  
<223> X = L or S or R

<220>  
<221> MISC\_FEATURE  
<222> (145)..(145)  
<223> X = S or F

<220>  
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<222> (147)..(147)  
<223> X = F or Y

<220>  
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<222> (148)..(148)  
<223> X = T or A

<220>  
<221> MISC\_FEATURE  
<222> (149)..(149)  
<223> X = A or S

<220>  
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<222> (150)..(150)  
<223> X = V or I

<220>  
<221> MISC\_FEATURE  
<222> (151)..(151)  
<223> X = T or C

<220>  
<221> MISC\_FEATURE

<222> (152)..(152)  
<223> X = N or S

<220>  
<221> MISC\_FEATURE  
<222> (153)..(153)  
<223> X = F or V

<220>  
<221> MISC\_FEATURE  
<222> (156)..(156)  
<223> X = S or D

<220>  
<221> MISC\_FEATURE  
<222> (157)..(157)  
<223> X = L or V

<220>  
<221> MISC\_FEATURE  
<222> (164)..(164)  
<223> X = N or Q

<220>  
<221> MISC\_FEATURE  
<222> (179)..(179)  
<223> X = V or I

<400> 2

Ser Xaa Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His  
1 5 10 15

Xaa Pro Leu His Pro Ala Ala Met Pro His Leu Leu Xaa Gly Ser Ser  
20 25 30

Gly Leu Xaa Arg Tyr Val Ala Arg Leu Ser Ser Xaa Ser Xaa Xaa Xaa  
35 40 45

Asn Xaa Gln Xaa Xaa Xaa Xaa Xaa Xaa Leu His Xaa Xaa Cys Ser Arg  
50 55 60

Xaa Leu Tyr Val Ser Leu Xaa Leu Leu Tyr Xaa Thr Xaa Gly Xaa Lys  
65 70 75 80

Leu His Leu Xaa Xaa His Pro Ile Xaa Leu Gly Phe Arg Lys Xaa Pro

85

90

95

Met Gly Xaa Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala  
100 105 110

Ile Xaa Xaa Xaa Xaa Xaa Arg Ala Phe Xaa His Cys Xaa Xaa Phe Xaa  
115 120 125

Tyr Met Asp Asp Xaa Val Leu Gly Ala Xaa Xaa Xaa Xaa His Xaa Glu  
130 135 140

Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Leu Xaa Xaa Gly Ile His  
145 150 155 160

Leu Asn Pro Xaa Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met  
165 170 175

Gly Tyr Xaa Ile Gly  
180

<210> 3  
<211> 23  
<212> DNA  
<213> artificial sequence

<220>  
<223> OS1 primer

<400> 3  
gcctcatttt gtgggtcacc ata

23

<210> 4  
<211> 18  
<212> DNA  
<213> artificial sequence

<220>  
<223> TTA3 primer

<400> 4  
aaattcgcag tccccaaa

18

<210> 5  
<211> 21  
<212> DNA  
<213> artificial sequence

<220>

<223> JM primer

<400> 5  
ttgggggtgga gccctcaggc t 21

<210> 6  
<211> 18  
<212> DNA  
<213> artificial sequence

<220>  
<223> TTA4 primer

<400> 6  
gaaaattggt aacagcgg 18

<210> 7  
<211> 20  
<212> DNA  
<213> artificial sequence

<220>  
<223> OS2 primer

<400> 7  
tctctgacat actttccaat 20

<210> 8  
<211> 23  
<212> DNA  
<213> artificial sequence

<220>  
<223> sense primer

<400> 8  
gcctcat ttt gtgggtcacc ata 23

<210> 9  
<211> 20  
<212> DNA  
<213> artificial sequence

<220>  
<223> antisense primer

<400> 9  
tctctgacat actttccaat 20

<210> 10  
<211> 18  
<212> DNA

<213> artificial sequence

<220>

<223> internal regions primer

<400> 10  
tgcacgattc ctgctcaa 18

<210> 11  
<211> 20  
<212> DNA  
<213> artificial sequence

<220>

<223> internal regions primer

<400> 11  
tttctcaaag gtggagacag 20

<210> 12  
<211> 18  
<212> DNA  
<213> artificial sequence

<220>

<223> PC1 forward primer

<400> 12  
gggaggagat taggttaa 18

<210> 13  
<211> 20  
<212> DNA  
<213> artificial sequence

<220>

<223> PC2 reverse primer

<400> 13  
ggcaaaaacg agagtaactc 20

<210> 14  
<211> 42  
<212> DNA  
<213> artificial sequence

<220>

<223> HBV-specific molecular beacon primer

<220>

<221> misc\_feature

<222> (42)..(42)

<223> n = L

<400> 14  
cgcgctcctac tgttcaagcc tccaagctgt gacgcgdabc yn

42

<210> 15  
<211> 280  
<212> DNA  
<213> artificial sequence

<220>  
<223> ILA 1 F, A-E

<220>  
<221> misc\_feature  
<222> (215)..(215)  
<223> n = any nucleotide

<400> 15  
tggctcagtt tactagtgcc atttgttcag tggttcgtag ggctttcccc cactgtttgg 60  
ctttcagtta tatggatgat gtggtattgg gggccaagtc tgtayagcay cttgagtc 120  
tttttaccgc tgttaccaat tttcttttgt ctttgggtat acatttaaac cctaacaaaa 180  
ctaaaagatg gggttactct ttacatttca tgggntatgt cattggatgt tatgggtcat 240  
tgccacaaga tcacatcata cagaaaatca aagatggttt 280

<210> 16  
<211> 242  
<212> DNA  
<213> artificial sequence

<220>  
<223> ILA 2 F, A-E

<400> 16  
tggctcagtt tactagtgcc atttgttcag tggttcgtag ggctttcccc cactgtttgg 60  
ctttcagtta tatggatgat gtggtattgg gggccaagtc tgtacagcat cttgagtc 120  
tttttaccgc tgttaccaat tttcttttgt ctttgggtat acatttaaac cctaacaaaa 180  
caaagagatg gggttactct ctaaatttta tgggttatgt cattggatgt tatgggtcct 240  
tg 242

<210> 17  
<211> 277  
<212> DNA  
<213> artificial sequence

<220>

<223> ILA 3 F, A-E

<400> 17

tggtcagtt tactagtgcc atttgttcag tggttcgtag ggctttcccc cactgtttgg 60  
ctttcagtta tatggatgat gtggtattgg gggccaagtc tgtacagcat cttgagtccc 120  
tttttaccgc tgttaccaat tttcttttgt ctttgggtat acatttaaac cctaacaaaa 180  
caaagagatg gggttactct ctaaatttta tgggttatgt cattggatgt tatgggtcct 240  
tgccacaaga acacatcata caaaaaatca aagaatg 277

<210> 18

<211> 237

<212> DNA

<213> artificial sequence

<220>

<223> ILA 4 F, A-E

<400> 18

tggtcagtt tactagtgcc atttgttcag tggttcgtag ggctttcccc cactgtttgg 60  
ctttcagtta tatggatgat gtggtattgg gggccaagtc tgtacagcat cttgagtccc 120  
tttttaccgc tgttaccaat tttcttttgt ctttgggcat acatttaaac cctaacaaaa 180  
ctaaaagatg ggggtactct ttaaatttca tgggatatgt cattggatgg tatgggg 237

<210> 19

<211> 336

<212> PRT

<213> artificial sequence

<220>

<223> Pol Trans Pre 1

<220>

<221> MISC\_FEATURE

<222> (11)..(11)

<223> x = any amino acid

<220>

<221> MISC\_FEATURE

<222> (17)..(17)

<223> x = any amino acid

<220>

<221> MISC\_FEATURE

<222> (38)..(38)

<223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (46)..(46)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (50)..(50)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (101)..(101)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (208)..(208)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (295)..(295)  
 <223> x = any amino acid

<400> 19

Lys	Leu	Ala	Ser	Lys	Ser	Ala	Ser	Ser	Ile	Xaa	Gln	Ser	Pro	Val	Arg
1				5					10					15	

Xaa	Ala	Ala	Tyr	Pro	Ala	Val	Ser	Thr	Phe	Glu	Lys	His	Ser	Ser	Ser
			20					25					30		

Gly	His	Ala	Val	Glu	Xaa	His	Asn	Leu	Pro	Pro	Asn	Ser	Xaa	Arg	Ser
			35				40					45			

Gln	Xaa	Glu	Arg	Pro	Val	Phe	Pro	Cys	Trp	Trp	Leu	Gln	Phe	Arg	Asn
	50					55					60				

Ser	Lys	Pro	Cys	Ser	Asp	Tyr	Cys	Leu	Ser	His	Ile	Val	Asn	Leu	Leu
65					70					75				80	

Glu	Asp	Trp	Gly	Pro	Cys	Ala	Glu	His	Gly	Glu	His	His	Ile	Arg	Ile
				85					90					95	



Pro Arg Thr Pro Xaa Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys  
100 105 110

Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln  
115 120 125

Phe Ser Arg Gly Asn Tyr Arg Val Ser Trp Pro Lys Phe Ala Val Pro  
130 135 140

Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu  
145 150 155 160

Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu Pro Leu His Pro Ala  
165 170 175

Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val  
180 185 190

Ala Arg Leu Ser Ser Asn Ser Arg Ile Phe Asn His Gln Arg Gly Xaa  
195 200 205

Met Gln Asn Leu His Asp Tyr Cys Ser Arg Asn Leu Tyr Val Ser Leu  
210 215 220

Leu Leu Leu Tyr Gln Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His  
225 230 235 240

Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser  
245 250 255

Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg  
260 265 270

Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val  
275 280 285

Leu Gly Ala Lys Ser Val Xaa His Leu Glu Ser Leu Phe Thr Ala Val  
290 295 300

Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr  
305 310 315 320

Lys Arg Trp Gly Tyr Ser Leu His Phe Met Gly Tyr Val Ile Gly Cys  
 325 330 335

<210> 20  
 <211> 340  
 <212> PRT  
 <213> artificial sequence

<220>  
 <223> Pol Trans 2

<400> 20

His Thr Thr Asn Phe Ala Ser Lys Ser Ala Ser Cys Leu His Gln Ser  
 1 5 10 15

Pro Val Arg Lys Ala Ala Tyr Pro Ala Val Ser Thr Phe Glu Lys His  
 20 25 30

Ser Ser Ser Gly His Ala Val Glu Phe His Asn Leu Pro Pro Asn Ser  
 35 40 45

Ala Arg Ser Gln Ser Glu Arg Pro Val Phe Pro Cys Trp Trp Leu Gln  
 50 55 60

Phe Arg Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu Ser Leu Ile Val  
 65 70 75 80

Asn Leu Leu Glu Asp Trp Gly Pro Cys Ala Glu His Gly Glu His His  
 85 90 95

Ile Arg Ile Pro Arg Thr Pro Ser Arg Val Thr Gly Gly Val Phe Leu  
 100 105 110

Val Asp Lys Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp  
 115 120 125

Phe Ser Gln Phe Ser Arg Gly Asn Tyr Arg Val Ser Trp Pro Lys Phe  
 130 135 140

Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu  
 145 150 155 160

Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu Pro Leu  
 165 170 175

His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Ser  
180 185 190

Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Leu Asn Asn Gln  
195 200 205

His Gly Thr Met Pro Asp Leu His Asp Tyr Cys Ser Arg Asn Leu Tyr  
210 215 220

Val Ser Leu Leu Leu Leu Tyr Gln Thr Phe Gly Arg Lys Leu His Leu  
225 230 235 240

Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val  
245 250 255

Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser  
260 265 270

Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp  
275 280 285

Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe  
290 295 300

Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro  
305 310 315 320

Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val  
325 330 335

Ile Gly Cys Tyr  
340

<210> 21  
<211> 344  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans 3

<400> 21

Leu Ala Gln Gly Ile Leu Gln Asn Phe Ala Ser Lys Ser Ala Ser Cys  
1 5 10 15

Leu His Gln Ser Pro Val Arg Lys Ala Ala Tyr Pro Ala Val Ser Thr  
 20 25 30

Phe Glu Lys His Ser Ser Ser Gly His Ala Val Glu Phe His Asn Leu  
 35 40 45

Pro Pro Asn Ser Ala Arg Ser Gln Ser Glu Arg Pro Val Phe Pro Cys  
 50 55 60

Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu  
 65 70 75 80

Ser Leu Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Cys Ala Glu His  
 85 90 95

Gly Glu His His Ile Arg Ile Pro Arg Thr Pro Ser Arg Val Thr Gly  
 100 105 110

Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr Ala Glu Ser Arg  
 115 120 125

Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Asn Tyr Arg Val Ser  
 130 135 140

Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu  
 145 150 155 160

Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr  
 165 170 175

His Leu Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser  
 180 185 190

Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile  
 195 200 205

Leu Asn Asn Gln His Gly Thr Met Pro Asp Leu His Asp Tyr Cys Ser  
 210 215 220

Arg Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Gln Thr Phe Gly Arg  
 225 230 235 240

Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile  
245 250 255

Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser  
260 265 270

Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe  
275 280 285

Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu  
290 295 300

Glu Ser Leu Phe Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile  
305 310 315 320

His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe  
325 330 335

Met Gly Tyr Val Ile Gly Cys Tyr  
340

<210> 22  
<211> 336  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans 4

<220>  
<221> MISC\_FEATURE  
<222> (24)..(24)  
<223> x =any amino acid

<400> 22

Ala Ser Lys Ser Ala Ser Ser Ile Tyr Gln Ser Pro Val Gly Thr Ala  
1 5 10 15

Ala Tyr Pro Ala Val Ser Thr Xaa Glu Lys His Ser Ser Ser Gly His  
20 25 30

Ala Val Glu Leu His Asn Leu Pro Pro Asn Ser Glu Arg Ser Gln Gly  
35 40 45

Glu Arg Pro Val Phe Pro Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys  
50 55 60

Pro Cys Ser Asp Tyr Cys Leu Ser His Ile Val Asn Leu Leu Glu Asp  
65 70 75 80

Trp Gly Pro Cys Ala Glu His Gly Glu His His Ile Arg Ile Pro Arg  
85 90 95

Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro  
100 105 110

His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser  
115 120 125

Arg Gly Asn Tyr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu  
130 135 140

Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu  
145 150 155 160

Asp Val Ser Ala Ala Phe Tyr His Leu Pro Leu His Pro Ala Ala Met  
165 170 175

Pro His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg  
180 185 190

Leu Ser Ser Asn Ser Arg Ile Phe Asn His Gln Arg Gly Asn Met Gln  
195 200 205

Asn Leu His Asp Cys Cys Ser Arg Asn Leu Tyr Val Ser Leu Leu Leu  
210 215 220

Leu Tyr Gln Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile  
225 230 235 240

Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe  
245 250 255

Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala  
260 265 270

Phe Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly

275

280

285

Ala Lys Ser Val Gln His Leu Glu Ser Leu Phe Thr Ala Val Thr Asn  
290 295 300

Phe Leu Leu Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg  
305 310 315 320

Trp Gly Tyr Ser Leu Asn Phe Met Gly Tyr Val Ile Gly Trp Tyr Gly  
325 330 335

<210> 23  
<211> 226  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of Pre 1

<220>  
<221> MISC\_FEATURE  
<222> (120)..(120)  
<223> x = any amino acid

<220>  
<221> MISC\_FEATURE  
<222> (208)..(208)  
<223> x = any amino acid

<400> 23

Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu Val Leu Gln  
1 5 10 15

Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu  
20 25- 30

Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr Thr Val Cys  
35 40 45

Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser Pro Thr Ser  
50 55 60

Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe  
65 70 75 80

Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val  
85 90 95

Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro Gly  
100 105 110

Ser Ser Thr Thr Ser Ala Gly Xaa Cys Arg Thr Cys Thr Thr Thr Ala  
115 120 125

Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp  
130 135 140

Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys  
145 150 155 160

Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu  
165 170 175

Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu  
180 185 190

Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Ser Xaa  
195 200 205

Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val  
210 215 220

Tyr Ile  
225

<210> 24  
<211> 309  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of 2

<400> 24

Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro  
1 5 10 15

Leu Ser Pro Pro Leu Arg Asn Thr His Pro Gln Ala Met Gln Trp Asn  
20 25 30



Ser Thr Thr Phe His Gln Thr Leu Gln Asp Pro Arg Val Arg Gly Leu  
35 40 45

Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Leu  
50 55 60

Thr Thr Ala Ser Pro Leu Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro  
65 70 75 80

Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu  
85 90 95

Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro  
100 105 110

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr  
115 120 125

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
130 135 140

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
145 150 155 160

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
165 170 175

Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu  
180 185 190

Ile Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Arg Thr Cys Met  
195 200 205

Thr Thr Ala Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr Lys  
210 215 220

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
225 230 235 240

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
245 250 255

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
260 265 270

Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
275 280 285

Tyr Ser Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys  
290 295 300

Leu Trp Val Tyr Ile  
305

<210> 25  
<211> 309  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of 3

<400> 25

Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro  
1 5 10 15

Leu Ser Pro Pro Leu Arg Asn Thr His Pro Gln Ala Met Gln Trp Asn  
20 25 30

Ser Thr Thr Phe His Gln Thr Leu Gln Asp Pro Arg Val Arg Gly Leu  
35 40 45

Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Leu  
50 55 60

Thr Thr Ala Ser Pro Leu Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro  
65 70 75 80

Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu  
85 90 95

Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro  
100 105 110

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr  
115 120 125

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
130 135 140

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
145 150 155 160

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
165 170 175

Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu  
180 185 190

Ile Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Arg Thr Cys Met  
195 200 205

Thr Thr Ala Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr Lys  
210 215 220

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
225 230 235 240

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
245 250 255

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
260 265 270

Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
275 280 285

Tyr Ser Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys  
290 295 300

Leu Trp Val Tyr Ile  
305

<210> 26  
<211> 309  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of 4

<220>  
<221> MISC\_FEATURE  
<222> (21)..(21)  
<223> x = any amino acid

<220>  
<221> MISC\_FEATURE  
<222> (46)..(46)  
<223> x = any amino acid

<400> 26

Pro Pro Pro Pro Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro  
1 5 10 15

Leu Ser Pro Pro Xaa Arg Asn Thr His Pro Gln Ala Met Gln Trp Asn  
20 25 30

Ser Thr Thr Phe His Gln Thr Leu Lys Asp Pro Arg Val Xaa Gly Leu  
35 40 45

Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro  
50 55 60

Thr Thr Ala Ser Pro Ile Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro  
65 70 75 80

Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro Leu Leu  
85 90 95

Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro  
100 105 110

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly Gly Thr  
115 120 125

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
130 135 140

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
145 150 155 160

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
165 170 175

Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu  
180 185 190

Ile Pro Gly Ser Ser Thr Thr Ser Ala Gly Thr Cys Arg Thr Cys Thr  
195 200 205

Thr Ala Ala Gln Gly Thr Ser Met Tyr Pro Ser Cys Cys Cys Thr Lys  
210 215 220

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
225 230 235 240

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
245 250 255

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
260 265 270

Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
275 280 285

Tyr Ser Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys  
290 295 300

Leu Trp Ala Tyr Ile  
305

<210> 27  
<211> 656  
<212> DNA  
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<220>  
<223> S0

<220>  
<221> misc\_feature  
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<223> n = any nucleotide

<400> 27  
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gtcctgggta tcgctggatg tgtctgcggc gttttatcat cttcctcttc atcctgctgc 180

tatgcctcat cttcttgttg gttcttcttg actgtcaagg tatgttgccc gtttgcctc	240
taattccagg atcctcaacc accagcacgg gaccatgccg aacctgcacg actcctgctc	300
aaggaacctc tacgggtccc tcatgttgct gtaccaaacc ttoggacgga aattgcacct	360
gtattcccat cccatcatcc tgggctttcg gaaaattcct atgggagtgg gcctcagccc	420
gtttctcctg gctcagttta ctagtgccat ttgttcagtg gttcgtaggg ctttccccc	480
ctgtctggct tttagttata tggatgatgt ggtattgggg gccaaagtctg tatcgcatct	540
tgagtccttt tttaccgctg ntaccaatth tcttttgtct ttgggtatac atttaaacc	600
taacaaaaca aaaagatggg gttactcct acattttatg ggctatgtca ttggat	656

<210> 28  
 <211> 625  
 <212> DNA  
 <213> artificial sequence

<220>  
 <223> S6

<220>  
 <221> misc\_feature  
 <222> (10)..(10)  
 <223> n = any nucleotide

<400> 28	
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ctgtcaaggt atgttgcccc tttgtcctct aattccagga tcttcaacca ccagcagggg	180
accatgccga acctgcacga ctctgtctca aggaacctct acggttcct catgttgctg	240
taccaaacct tcggacggaa attgcacctg tattcccatc ccatcatcct gggctttcgg	300
aaaattccta tgggagtggg cctcagccc tttctcatgg ctcagtttac tagtgccatt	360
tgttcagtgg ttcgtagggc tttccccac tgtctggctt ttggttatgt ggatgatgtg	420
gtattggggg ccaagtctgt atcgcatctt gaggcccttt ttaccgctgt taccaatth	480
cttttgtctt tgggtatata tttaaatcct aacaaaacaa aaagatgggg ttactcccta	540
cattttatgg gctatgtcat tggatgtcat gggtccttgc cacaagaaca catcagacaa	600
aaaatcaaag aatgttttag aaac	625

<210> 29

<211> 1033  
 <212> DNA  
 <213> artificial sequence

<220>  
 <223> S8

<400> 29  
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 aaaccctggt ccgactactg cctctcactc atcgtcaatc ttctcgagga ttgggggtccc 240  
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 ttctctcaat ttctgagggg ggactaccgt gtgtcttggc caaaattcgc agtccccaac 420  
 ctccaatcac tcaccaacct cctgtcctcc aacttgtcct ggttatcgct ggatgtgtct 480  
 gggcggtttt atcatcttcc tcttcactct gctgctatgc ctcatcttct tgttggttct 540  
 tctggactgt caaggatatgt tgcccgtttg tcctctaatt ccaggatcct caaccaccag 600  
 caggggacca tgccgaacct gcacgactcc tgctcaagga acctctacgg ttccctcatg 660  
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 gccatttggt cagtgggtcg tagggctttc cccactgtc tggcttttgg ttatgtggat 840  
 gatgtggtat tgggggcaa gtctgtatcg catcttgagt ccctttttac cgtgtgtacc 900  
 aattttcttt tgtctttggg tatacattta aatcctaaca aaacaaaaag atgggggttac 960  
 tccctacatt ttatgggcta tgctattgga tgctatgggt ccttgccaca agaacacatc 1020  
 agacaaaaaa tca 1033

<210> 30  
 <211> 1100  
 <212> DNA  
 <213> artificial sequence

<220>  
 <223> S12

<400> 30  
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ctcatcctca ggccatgcag tggaactcaa caaccttcca ccaaactctg caagatccca	180
gagtgaagagg cctgtatttc cctgctgggtg gctccagttc aggaacagta aaccctgttc	240
cgactactgc ctctcactca tcgtcaatct tctcgaggat tgggggtccct gcgctgaaca	300
tggagaacat cacatcagga ctctaggac cccttctcgt gttacaggcg gggttttttot	360
tggtgacaag aatcctcaca ataccgcaga gtctagactc gtggtggact tctctcaatt	420
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tcattcttct cttcatcctg ctgctatgcc tcattctctt gttggttctt ctggactgtc	600
aaggatatgtt gcccgtttgt cctctaattc caggatcctc aaccaccagc aggggaccat	660
gccgaacctg cacgactcct gctcaaggaa cctctacggg tccctcatgt tgctgtacca	720
aaccttcgga cggaaattgc acctgtattc ccatcccatc atcctgggct ttcggaaaat	780
tcctatggga gtgggcctca gcccgtttct catggctcag ttactagtgc ccatttgttc	840
agtggttcgt agggcctttcc cccactgtct ggcttttggt tatgtggatg atgtggtatt	900
ggggggccaag tctgtatcgc atcttgagtc cctttttacc gctgttacca attttctttt	960
gtctttgggt atacatttaa atcctaacaa aacaaaaaga tgggggttact ccctacattt	1020
tatgggctat gtcattggat gtcattgggtc cttgccacaa gaacacatca gacaaaaaat	1080
caaagaatgt tttagaaaac	1100

<210> 31  
 <211> 987  
 <212> DNA  
 <213> artificial sequence

<220>  
 <223> S15

<220>  
 <221> misc\_feature  
 <222> (329)..(329)  
 <223> y = any nucleotide

<220>  
 <221> misc\_feature  
 <222> (943)..(943)  
 <223> y = any nucleotide

<400> 31



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caaccttcca ccaaactctg caagatccca gagtgaaagg cctgtatttc cctgctggtg	180
gtccagttc aggaacagta aaccctgttc cgactactgc ctctcactca tcgtcaatct	240
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cccttctcgt gttacaggcg gggtttttyt tgttgacaag aatcctcaca ataccgcaga	360
gtctagactc gtggtggact tctctcaatt ttcgaggggg gactaccgtg tgtcttggcc	420
aaaattcgca gtccccaacc tccaatcact caccaacctc ctgtcctcca acttgctctg	480
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tcatcttctt gttggctcta ctggactgtc aaggatgtt gcccgtttgt cctctaattc	600
caggatctc aaccaccagc aggggacct gccgaacctg cagactcct gctcaaggaa	660
cctctacggt tccctcatgt tgctgtacca aaccttcgga cggaaattgc acctgtattc	720
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<210> 32  
 <211> 350  
 <212> PRT  
 <213> artificial sequence

<220>  
 <223> Pol Trans S0

<220>  
 <221> MISC\_FEATURE  
 <222> (309)..(309)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (345)..(345)  
 <223> x = any amino acid

<400> 32

Ser Gly His Thr Thr Asn Phe Ala Ser Lys Ser Thr Ser Cys Leu His  
1 5 10 15

Gln Ser Pro Val Arg Lys Ala Ala Tyr Pro Ala Val Ser Thr Phe Glu  
20 25 30

Arg His Ser Ser Ser Gly His Ala Val Glu Leu Asn Asn Leu Pro Pro  
35 40 45

Asn Ser Ala Arg Ser Gln Ser Glu Arg Pro Val Phe Pro Cys Trp Trp  
50 55 60

Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu Ser Leu  
65 70 75 80

Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Cys Ala Glu His Gly Glu  
85 90 95

His His Ile Arg Thr Pro Arg Thr Pro Ser Arg Val Thr Gly Gly Val  
100 105 110

Phe Leu Val Asp Lys Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val  
115 120 125

Val Asp Phe Ser Gln Phe Ser Arg Gly Asp Tyr Arg Val Ser Trp Pro  
130 135 140

Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser  
145 150 155 160

Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu  
165 170 175

Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly  
180 185 190

Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Leu Asn  
195 200 205

His Gln His Gly Thr Met Pro Asn Leu His Asp Ser Cys Ser Arg Asn  
210 215 220

Leu Tyr Gly Ser Leu Met Leu Leu Tyr Gln Thr Phe Gly Arg Lys Leu

225 230 235 240

His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met  
245 250 255

Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile  
260 265 270

Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser Tyr  
275 280 285

Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Ser His Leu Glu Ser  
290 295 300

Leu Phe Thr Ala Xaa Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu  
305 310 315 320

Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu His Phe Met Gly  
325 330 335

Tyr Val Ile Gly Cys His Gly Ser Xaa Pro Gln Glu His Ile  
340 345 350

<210> 33  
<211> 181  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans S6

<400> 33

Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His  
1 5 10 15

Leu Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser  
20 25 30

Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Leu  
35 40 45

Asn His Gln Gln Gly Thr Met Pro Asn Leu His Asp Ser Cys Ser Arg  
50 55 60

Asn Leu Tyr Gly Ser Leu Met Leu Leu Tyr Gln Thr Phe Gly Arg Lys  
65 70 75 80

Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro  
85 90 95

Met Gly Val Gly Leu Ser Pro Phe Leu Met Ala Gln Phe Thr Ser Ala  
100 105 110

Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Gly  
115 120 125

Tyr Val Asp Asp Val Val Leu Gly Ala Lys Ser Val Ser His Leu Glu  
130 135 140

Ser Leu Phe Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His  
145 150 155 160

Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu His Phe Met  
165 170 175

Gly Tyr Val Ile Gly  
180

<210> 34  
<211> 340  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans S8

<400> 34

Cys Pro Phe Cys Leu His Gln Ser Pro Val Arg Lys Ala Ala Tyr Pro  
1 5 10 15

Ala Val Ser Thr Phe Glu Arg His Ser Ser Ser Gly His Ala Val Glu  
20 25 30

Leu Asn Asn Leu Pro Pro Asn Ser Ala Arg Ser Gln Ser Glu Arg Pro  
35 40 45

Val Phe Pro Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser  
50 55 60

Asp Tyr Cys Leu Ser Leu Ile Val Asn Leu Leu Glu Asp Trp Gly Pro  
65 70 75 80

Cys Ala Glu His Gly Glu His His Ile Arg Thr Pro Arg Thr Pro Ser  
85 90 95

Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His Asn Thr  
100 105 110

Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg Gly Asp  
115 120 125

Tyr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln Ser Leu  
130 135 140

Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser  
145 150 155 160

Ala Ala Phe Tyr His Leu Pro Leu His Pro Ala Ala Met Pro His Leu  
165 170 175

Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser  
180 185 190

Asn Ser Arg Ile Leu Asn His Gln Gln Gly Thr Met Pro Asn Leu His  
195 200 205

Asp Ser Cys Ser Arg Asn Leu Tyr Gly Ser Leu Met Leu Leu Tyr Gln  
210 215 220

Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile Leu Gly  
225 230 235 240

Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Met Ala  
245 250 255

Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His  
260 265 270

Cys Leu Ala Phe Gly Tyr Val Asp Asp Val Val Leu Gly Ala Lys Ser  
275 280 285

Val Ser His Leu Glu Ser Leu Phe Thr Ala Val Thr Asn Phe Leu Leu  
290 295 300

Ser Leu Gly Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr  
305 310 315 320

Ser Leu His Phe Met Gly Tyr Val Ile Gly Cys His Gly Ser Leu Pro  
325 330 335

Gln Glu His Ile  
340

<210> 35  
<211> 340  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans S12

<400> 35

Ser Gly His Ile Thr Asn Ser Ala Ser Lys Ser Thr Ser Cys Leu His  
1 5 10 15

Gln Ser Pro Val Arg Lys Ala Ala Tyr Pro Ala Val Ser Thr Phe Glu  
20 25 30

Arg His Ser Ser Ser Gly His Ala Val Glu Leu Asn Asn Leu Pro Pro  
35 40 45

Asn Ser Ala Arg Ser Gln Ser Glu Arg Pro Val Phe Pro Cys Trp Trp  
50 55 60

Leu Gln Phe Arg Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu Ser Leu  
65 70 75 80

Ile Val Asn Leu Leu Glu Asp Trp Gly Pro Cys Ala Glu His Gly Glu  
85 90 95

His His Ile Arg Thr Pro Arg Thr Pro Ser Arg Val Thr Gly Gly Val  
100 105 110

Phe Leu Val Asp Lys Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val  
115 120 125

Val Asp Phe Ser Gln Phe Ser Arg Gly Asp Tyr Arg Val Ser Trp Pro  
130 135 140

Lys Phe Ala Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser  
145 150 155 160

Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu  
165 170 175

Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly  
180 185 190

Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Leu Asn  
195 200 205

His Gln Gln Gly Thr Met Pro Asn Leu His Asp Ser Cys Ser Arg Asn  
210 215 220

Leu Tyr Gly Ser Leu Met Leu Leu Tyr Gln Thr Phe Gly Arg Lys Leu  
225 230 235 240

His Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met  
245 250 255

Gly Val Gly Leu Ser Pro Phe Leu Met Ala Gln Phe Thr Ser Ala Ile  
260 265 270

Cys Ser Val Val Arg Arg Ala Phe Pro-His Cys Leu Ala Phe Gly Tyr  
275 280 285

Val Asp Asp Val Val Leu Gly Ala Lys Ser Val Ser His Leu Glu Ser  
290 295 300

Leu Phe Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His Leu  
305 310 315 320

Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu His Phe Met Gly  
325 330 335

Tyr Val Ile Gly  
340

<210> 36  
 <211> 328  
 <212> PRT  
 <213> artificial sequence

<220>  
 <223> Pol Trans S15

<220>  
 <221> MISC\_FEATURE  
 <222> (110)..(110)  
 <223> x = any amino acid

<220>  
 <221> MISC\_FEATURE  
 <222> (314)..(314)  
 <223> x = any amino acid

<400> 36

Thr Asn Phe Ala Ser Lys Ser Thr Ser Cys Leu His Gln Ser Pro Val  
 1 5 10 15

Arg Lys Ala Ala Tyr Pro Ala Val Ser Thr Phe Glu Arg His Ser Ser  
 20 25 30

Ser Gly His Ala Val Glu Leu Asn Asn Leu Pro Pro Asn Ser Ala Arg  
 35 40 45

Ser Gln Ser Glu Arg Pro Val Phe Pro Cys Trp Trp Leu Gln Phe Arg  
 50 55 60

Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu Ser Leu Ile Val Asn Leu  
 65 70 75 80

Leu Glu Asp Trp Gly Pro Cys Ala Glu His Gly Glu His His Ile Arg  
 85 90 95

Thr Pro Arg Thr Pro Ser Arg Val Thr Gly Gly Val Phe Xaa Val Asp  
 100 105 110

Lys Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser  
 115 120 125

Gln Phe Ser Arg Gly Asp Tyr Arg Val Ser Trp Pro Lys Phe Ala Val  
 130 135 140



Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser Trp  
145 150 155 160

Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Leu Pro Leu His Pro  
165 170 175

Ala Ala Met Pro His Leu Leu Val Gly Ser Thr Gly Leu Ser Arg Tyr  
180 185 190

Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Leu Asn His Gln Gln Gly  
195 200 205

Thr Met Pro Asn Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Gly Ser  
210 215 220

Leu Met Leu Leu Tyr Gln Thr Phe Gly Arg Lys Leu His Leu Tyr Ser  
225 230 235 240

His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu  
245 250 255

Ser Pro Phe Leu Met Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Val  
260 265 270

Arg Arg Ala Phe Pro His Cys Leu Ala Phe Gly Tyr Val Asp Asp Val  
275 280 285

Val Leu Gly Ala Lys Ser Val Ser His Leu Glu Ser Leu Phe Thr Ala  
290 295 300

Val Thr Asn Phe Leu Leu Ser Leu Gly Xaa His Leu Asn Pro Asn Lys  
305 310 315 320

Thr Lys Arg Trp Gly Tyr Ser Leu  
325

<210> 37  
<211> 197  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of S0

<220>  
 <221> MISC\_FEATURE  
 <222> (187)..(187)  
 <223> x = any amino acid

<400> 37

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Arg Gly Gly Thr  
 1 5 10 15

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
 20 25 30

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
 35 40 45

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
 50 55 60

Leu Leu Val Leu Leu Asp Cys Gln Gly Met Leu Pro Val Cys Pro Leu  
 65 70 75 80

Ile Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Arg Thr Cys Thr  
 85 90 95

Thr Pro Ala Gln Gly Thr Ser Thr Val Pro Ser Cys Cys Cys Thr Lys  
 100 105 110

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
 115 120 125

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
 130 135 140

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
 145 150 155 160

Val Trp Leu Leu Val Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
 165 170 175

Tyr Arg Ile Leu Ser Pro Phe Leu Pro Leu Xaa Pro Ile Phe Phe Cys  
 180 185 190

Leu Trp Val Tyr Ile

195

<210> 38  
 <211> 161  
 <212> PRT  
 <213> artificial sequence

<220>  
 <223> HBsAg Trans of S6

<400> 38

Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile  
 1 5 10 15

Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu  
 20 25 30

Leu Asp Cys Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro Gly Ser  
 35 40 45

Ser Thr Thr Ser Arg Gly Pro Cys Arg Thr Cys Thr Thr Pro Ala Gln  
 50 55 60

Gly Thr Ser Thr Val Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly  
 65 70 75 80

Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys Phe  
 85 90 95

Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu Val  
 100 105 110

Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Leu  
 115 120 125

Val Met Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Arg Ile Leu  
 130 135 140

Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr  
 145 150 155 160

Ile

<210> 39  
<211> 160  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of S8

<400> 39

Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile  
1 5 10 15

Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu  
20 25 30

Asp Cys Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro Gly Ser Ser  
35 40 45

Thr Thr Ser Arg Gly Pro Cys Arg Thr Cys Thr Thr Pro Ala Gln Gly  
50 55 60

Thr Ser Thr Val Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn  
65 70 75 80

Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys Phe Leu  
85 90 95

Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu Ser Leu Leu Val Pro  
100 105 110

Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Leu Val  
115 120 125

Met Trp Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Arg Ile Leu Ser  
130 135 140

Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile  
145 150 155 160

<210> 40  
<211> 325  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of S12

<400> 40

Leu Gly Ser Pro Gln Ala Gln Gly Ile Leu Gln Thr Leu Pro Ala Asn  
1 5 10 15

Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro  
20 25 30

Leu Ser Pro Pro Leu Arg Asp Thr His Pro Gln Ala Met Gln Trp Asn  
35 40 45

Ser Thr Thr Phe His Gln Thr Leu Gln Asp Pro Arg Val Lys Gly Leu  
50 55 60

Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro  
65 70 75 80

Thr Thr Ala Ser His Ser Ser Ser Ile Phe Ser Arg Ile Gly Val Pro  
85 90 95

Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Leu Leu Gly Pro Leu Leu  
100 105 110

Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro  
115 120 125

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Arg Gly Gly Thr  
130 135 140

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
145 150 155 160

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
165 170 175

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
180 185 190

Leu Leu Val Leu Leu Asp Cys Gln Gly Met Leu Pro Val Cys Pro Leu  
195 200 205

Ile Pro Gly Ser Ser Thr Thr Ser Arg Gly Pro Cys Arg Thr Cys Thr  
210 215 220

Thr Pro Ala Gln Gly Thr Ser Thr Val Pro Ser Cys Cys Cys Thr Lys  
225 230 235 240

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
245 250 255

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
260 265 270

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
275 280 285

Val Trp Leu Leu Val Met Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
290 295 300

Tyr Arg Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys  
305 310 315 320

Leu Trp Val Tyr Ile  
325

<210> 41  
<211> 309  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of S15

<220>  
<221> MISC\_FEATURE  
<222> (308)..(308)  
<223> x = any amino acid

<400> 41

Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser Gly Arg Gln Pro Thr Pro  
1 5 10 15

Leu Ser Pro Pro Leu Arg Asp Thr His Pro Gln Ala Met Gln Trp Asn  
20 25 30

Ser Thr Thr Phe His Gln Thr Leu Gln Asp Pro Arg Val Lys Gly Leu  
35 40 45

Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro Val Pro  
50 55 60

Thr Thr Ala Ser His Ser Ser Ser Ile Phe Ser Arg Ile Gly Val Pro  
65 70 75 80

Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Leu Leu Gly Pro Leu Leu  
85 90 95

Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr Ile Pro  
100 105 110

Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Arg Gly Gly Thr  
115 120 125

Thr Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr Ser Asn His Ser  
130 135 140

Pro Thr Ser Cys Pro Pro Thr Cys Pro Gly Tyr Arg Trp Met Cys Leu  
145 150 155 160

Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe  
165 170 175

Leu Leu Ala Leu Leu Asp Cys Gln Gly Met Leu Pro Val Cys Pro Leu  
180 185 190

Ile Pro Gly Ser Ser Thr Thr Ser Arg Gly Pro Cys Arg Thr Cys Thr  
195 200 205

Thr Pro Ala Gln Gly Thr Ser Thr Val Pro Ser Cys Cys Cys Thr Lys  
210 215 220

Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
225 230 235 240

Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser Trp Leu  
245 250 255

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
260 265 270

Val Trp Leu Leu Val Met Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
275 280 285

Tyr Arg Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe Phe Cys  
290 295 300

Leu Trp Val Xaa Ile  
305

<210> 42  
<211> 1031  
<212> DNA  
<213> artificial sequence

<220>  
<223> Nucleotide sequence of Patient C

<400> 42  
tactacaaac cttgccagca aatccgcctc ctgcctctac caatcgccag tcaggaaggc 60  
agcctacccc tctgactcca cctttgagaa acactcatcc tcaggccatg cagtggaaact 120  
ccacaaactt ccaccgaact ctacaagatc ccagagtgaaggcctgtat ctccctgctg 180  
gtggctccag ttcaggaaca gtaaaccctg ttccgactac tgtctctcac acatogtcaa 240  
tcttatcgag gattggggac cctgcactga acatggagaa catcacatca ggattcctag 300  
gacccctgct cgtgttacag gcggggtttt tcttgttgac aagaatcctc acaataccgc 360  
agagtctaga ctcggtgtgg acttctctca attttctagg ggggaccacc gtgtgccttg 420  
gccaaaattc gcagtcccca acctccaatc actcaccaac ctctgtcct ccaacttgtc 480  
ctgggttatcg ctggatgtgt ctgcggcgtt ttatcatatt cctcttcac ctgctgctat 540  
gcctcatctt cttgttggtt cttctggact atcaaggat gttgcccggt tgcctctaa 600  
ttccaggatc ctcaaccacc agcacgggac catgcagaac ctgcacgact cctgctcaag 660  
gaacctctwt gtatccctca tgttgctgta ccaaacctwc ggmcsaaat tgcacctgta 720  
ttcccatccc atcatcctgg gctttcggaa aattcctatg ggagtgggccc tcagcccggtt 780  
tctcctgact cagtttacta gtgccatttg ttcagtgggt cgtagggtt tccccactg 840  
tttggtttc agttatatgg atgatgtggt attggggggc aggtctgtac agcatcgtga 900  
ggcccttttt accgctgtta ccaattttct tttgtctctg ggtatacatt taaccccgga 960  
caaaaacaaa agatgggggtt actctttaca tttcatgggc tatgtcattg gatgttatgg 1020  
gtcattgccca c 1031



<210> 43  
<211> 316  
<212> PRT  
<213> artificial sequence

<220>  
<223> POL Trans of Patient

<400> 43

Thr Thr Asn Leu Ala Ser Lys Ser Ala Ser Cys Leu Tyr Gln Ser Pro  
1 5 10 15

Val Arg Lys Ala Ala Tyr Pro Ser Asp Ser Thr Phe Glu Lys His Ser  
20 25 30

Ser Ser Gly His Ala Val Glu Leu His Lys Leu Pro Pro Asn Ser Thr  
35 40 45

Arg Ser Gln Ser Glu Arg Pro Val Ser Pro Cys Trp Trp Leu Gln Phe  
50 55 60

Arg Asn Ser Lys Pro Cys Ser Asp Tyr Cys Leu Ser His Ile Val Asn  
65 70 75 80

Leu Ile Glu Asp Trp Gly Pro Cys Thr Glu His Gly Glu His His Ile  
85 90 95

Arg Ile Pro Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val  
100 105 110

Asp Lys Asn Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe  
115 120 125

Ser Gln Phe Ser Arg Gly Asp His Arg Val Pro Trp Pro Lys Phe Ala  
130 135 140

Val Pro Asn Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Ser  
145 150 155 160

Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His Ile Pro Leu His  
165 170 175

Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg  
180 185 190

Tyr Val Ala Arg Leu Pro Ser Asn Ser Arg Ile Leu Asn His Gln His  
195 200 205

Gly Thr Met Gln Asn Leu His Asp Ser Cys Ser Arg Asn Leu Tyr Phe  
210 215 220

Val Ser Leu Met Leu Leu Tyr Gln Thr Phe Thr Gly Arg Lys Leu His  
225 230 235 240

Leu Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly  
245 250 255

Val Gly Leu Ser Pro Phe Leu Leu Thr Gln Phe Thr Ser Ala Ile Cys  
260 265 270

Ser Ala Leu Phe Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile  
275 280 285

His Leu Thr Pro Asp Lys Thr Lys Arg Trp Gly Tyr Ser Leu His Phe  
290 295 300

Met Gly Tyr Val Ile Gly Cys Tyr Gly Ser Leu Pro  
305 310 315

<210> 44  
<211> 301  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of Patient C

<400> 44

Leu Gln Thr Leu Pro Ala Asn Pro Pro Pro Ala Ser Thr Asn Arg Gln  
1 5 10 15

Ser Gly Arg Gln Pro Thr Pro Leu Thr Pro Pro Leu Arg Asn Thr His  
20 25 30

Pro Gln Ala Met Gln Trp Asn Ser Thr Asn Phe His Arg Thr Leu Gln  
35 40 45

Asp Pro Arg Val Lys Gly Leu Tyr Leu Pro Ala Gly Gly Ser Ser Ser

50

55

60

Gly Thr Val Asn Pro Val Pro Thr Thr Val Ser His Thr Ser Ser Ile  
65 70 75 80

Leu Ser Arg Ile Gly Asp Pro Ala Leu Asn Met Glu Asn Ile Thr Ser  
85 90 95

Gly Phe Leu Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu  
100 105 110

Thr Arg Ile Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser  
115 120 125

Leu Asn Phe Leu Gly Gly Thr Thr Val Cys Leu Gly Gln Asn Ser Gln  
130 135 140

Ser Pro Thr Ser Asn His Ser Pro Thr Ser Cys Pro Pro Thr Cys Pro  
145 150 155 160

Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile  
165 170 175

Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln Gly  
180 185 190

Met Leu Pro Val Cys Pro Leu Ile Pro Gly Ser Ser Thr Thr Ser Thr  
195 200 205

Gly Pro Cys Arg Thr Cys Thr Thr Pro Ala Gln Gly Thr Ser Met Leu  
210 215 220

Tyr Pro Ser Cys Cys Cys Thr Lys Pro Ser Thr Ala Ala Asn Cys Thr  
225 230 235 240

Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Gly Lys Phe Leu Trp Glu  
245 250 255

Trp Ala Ser Ala Arg Phe Ser Leu Ser Leu Leu Val Pro Phe Val Gln  
260 265 270

Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val Ile Trp Met  
275 280 285

Met Trp Tyr Trp Gly Pro Gly Leu Tyr Ser Ile Val Arg  
290 295 300

<210> 45  
<211> 888  
<212> DNA  
<213> artificial sequence

<220>  
<223> Nucleotide sequence of Patient D

<400> 45  
tggtcacagt gccaacagtt cctcctcctg cctccaccaa tcggcagtca gggaggcagc 60  
ctactcccat ctctccacct ctaagagaca gtcctcctca ggccatggtg gctcagcctg 120  
ctggtgggtc cagttcagga aactcaacc ctgttcccaa tattgcctct cacatctcgt 180  
caatctcctt gaggactggg gaccctgccc cgaacatgga gaacatcaca tcaggattcc 240  
taggaccctt gctcgtgtta caggcggggg ttttcttggt gacaagaatc ctcaacaatac 300  
cgcagagtct agactcgtgg tggacttctc tcagttttct agggggatca cccgtgtgtc 360  
ttggccaaaa ttgcgagtc ccaacctcca atcactcacc aacctcctgt cctccaattt 420  
gacctgggta tcgctggata tgtctgcggc gttttatcat attcctcttc atcctgccgc 480  
tatgcctcat cttcttattg gttcttctgg attatcaagg tatgttgccc gtttgcctc 540  
taattccagg atccacaaca accagtgcgg gacctgcaa aacctgcacg actcctgctc 600  
aaggcaactc tatgtttccc tcatgttgct gtacaaaacc tacggatgga aattgcacct 660  
gtattcccat cccatcatct tgggctttcg caaaatacct atgggagtgg gcctcagtc 720  
gtttctcttg gctcagttta ctagtgccat ttgttcagtg attcgtaggg ctttcccca 780  
ctgtttggct ttcagctata ttgatgatgt ggtactgggg gccaaagtct cacaacatct 840  
tgagtcctt tataccgctg ttaccaattt tcttttgtct ttgggtat 888

<210> 46  
<211> 295  
<212> PRT  
<213> artificial sequence

<220>  
<223> Pol Trans of Patient D

<400> 46

Gly His Ser Ala Asn Ser Ser Ser Ser Cys Leu His Gln Ser Ala Val

1	5	10	15
Arg Glu Ala	Ala Tyr Ser His Leu Ser Thr Ser Lys Arg Gln Ser Ser		
20	25	30	
Ser Gly His Gly Gly Ser Ala Cys Trp Trp Leu Gln Phe Arg Asn Thr			
35	40	45	
Gln Pro Cys Ser Gln Tyr Cys Leu Ser His Leu Val Asn Leu Leu Glu			
50	55	60	
Asp Trp Gly Pro Cys Ala Glu His Gly Glu His His Ile Arg Ile Pro			
65	70	75	80
Arg Thr Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn			
85	90	95	
Pro His Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe			
100	105	110	
Ser Arg Gly Ile Thr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn			
115	120	125	
Leu Gln Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Thr Trp Leu Ser			
130	135	140	
Leu Asp Met Ser Ala Ala Phe Tyr His Ile Pro Leu His Pro Ala Ala			
145	150	155	160
Met Pro His Leu Leu Ile Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala			
165	170	175	
Arg Leu Ser Ser Asn Ser Arg Ile His Asn Asn Gln Cys Gly Thr Leu			
180	185	190	
Gln Asn Leu His Asp Ser Cys Ser Arg Gln Leu Tyr Val Ser Leu Met			
195	200	205	
Leu Leu Tyr Lys Thr Tyr Gly Trp Lys Leu His Leu Tyr Ser His Pro			
210	215	220	
Ile Ile Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro			
225	230	235	240

Phe Leu Leu Ala Gln Phe Thr Ser Ala Ile Cys Ser Val Ile Arg Arg  
245 250 255

Ala Phe Pro His Cys Leu Ala Phe Ser Tyr Ile Asp Asp Val Val Leu  
260 265 270

Gly Ala Lys Ser Ala Gln His Leu Glu Ser Leu Tyr Thr Ala Val Thr  
275 280 285

Asn Phe Leu Leu Ser Leu Gly  
290 295

<210> 47

<211> 293

<212> PRT

<213> artificial sequence

<220>

<223> HBsAg Trans of Patient D

<400> 47

Val Thr Val Pro Thr Val Pro Pro Pro Ala Ser Thr Asn Arg Gln Ser  
1 5 10 15

Gly Arg Gln Pro Thr Pro Ile Ser Pro Pro Leu Arg Asp Ser His Pro  
20 25 30

Gln Ala Met Val Ala Gln Pro Ala Gly Gly Ser Ser Ser Gly Thr Leu  
35 40 45

Asn Pro Val Pro Asn Ile Ala Ser His Ile Ser Ser Ile Ser Leu Arg  
50 55 60

Thr Gly Asp Pro Ala Pro Asn Met Glu Asn Ile Thr Ser Gly Phe Leu  
65 70 75 80

Gly Pro Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile  
85 90 95

Leu Thr Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Ser Phe  
100 105 110

Leu Gly Gly Ser Pro Val Cys Leu Gly Gln Asn Ser Gln Ser Pro Thr

115

120

125

Ser Asn His Ser Pro Thr Ser Cys Pro Pro Ile Pro Gly Tyr Arg Trp  
130 135 140

Ile Cys Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Pro Leu Cys  
145 150 155 160

Leu Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val  
165 170 175

Cys Pro Leu Ile Pro Gly Ser Thr Thr Thr Ser Ala Gly Pro Cys Lys  
180 185 190

Thr Cys Thr Thr Pro Ala Gln Gly Asn Ser Met Phe Pro Ser Cys Cys  
195 200 205

Cys Thr Lys Pro Thr Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser  
210 215 220

Ser Trp Ala Phe Ala Lys Tyr Leu Trp Glu Trp Ala Ser Val Arg Phe  
225 230 235 240

Ser Trp Leu Ser Leu Leu Val Pro Phe Val Gln Phe Val Gly Leu Ser  
245 250 255

Pro Thr Val Trp Leu Ser Ala Ile Leu Met Met Trp Tyr Trp Gly Pro  
260 265 270

Ser Leu His Asn Ile Leu Ser Pro Phe Ile Pro Leu Leu Pro Ile Phe  
275 280 285

Phe Cys Leu Trp Val  
290

<210> 48

<211> 591

<212> DNA

<213> artificial sequence

<220>

<223> Nucleotide sequence of Patient E

<400> 48

tctgtgctct caatttgtcc tggttatcgc tggatgtgtc tgcggcggtt tatgatattc

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ctcttcatcc tgctgctatg cctcatcttc ttattgggtc ttctggatta tcaaggatg      120
ttgcccgtct gtcctctaata tccaggatca acaacaacca gtacgggacc atgcaaaacc      180
aaaacctgca cgactcctgc tcaaggcaac tctatgtttc cctcatgttg ctgtacaaaa      240
cctacggatg gaaattgcac ctgtattccc atcccatcgt cctgggcttt cgcaaaattc      300
ctatgggagt gggcctcagt ccgtttctct tggctcagtt tactagtgcc atttggtcag      360
tggttcgtag ggctttcccc cactgtttgg ctttcagcta tatggatgat gtggtattgg      420
gggccaagtc tgtacagcat cgtgaggccc tttatacagc tgttaccaat tttcttttgt      480
ctctgggtat acatttaaac cctaacaaaa caaaaagatg gggttattcc ctaaacttca      540
tggtttacat aattggaagt tggggaacat tgccacagga tcatattgta c              591

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<210> 49
<211> 186
<212> PRT
<213> artificial sequence

<220>
<223> Pol Trans of Patient E

<400> 49

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```

Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr Asp
1      5      10      15

```

```

Ile Pro Leu His Pro Ala Ala Met Pro-His Leu Leu Ile Gly Ser Ser
      20      25      30

```

```

Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile Asn
      35      40      45

```

```

Asn Asn Gln Tyr Gly Thr Met Gln Asn Gln Asn Leu His Asp Ser Cys
      50      55      60

```

```

Ser Arg Gln Leu Tyr Val Ser Leu Met Leu Leu Tyr Lys Thr Tyr Gly
      65      70      75      80

```

```

Trp Lys Leu His Leu Tyr Ser His Pro Ile Val Leu Gly Phe Arg Lys
      85      90      95

```

```

Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr
      100      105      110

```



Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala  
115 120 125

Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His  
130 135 140

Arg Glu Ala Leu Tyr Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly  
145 150 155 160

Ile His Leu Asn Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn  
165 170 175

Phe Met Gly Tyr Ile Ile Gly Ser Trp Gly  
180 185

<210> 50  
<211> 165  
<212> PRT  
<213> artificial sequence

<220>  
<223> HBsAg Trans of Patient E

<400> 50

Ser Cys Pro Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg  
1 5 10 15

Phe Met Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu  
20 25 30

Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro  
35 40 45

Gly Ser Thr Thr Thr Ser Thr Gly Pro Cys Lys Thr Lys Thr Cys Thr  
50 55 60

Thr Pro Ala Gln Gly Asn Ser Met Phe Pro Ser Cys Cys Cys Thr Lys  
65 70 75 80

Pro Thr Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala  
85 90 95

Phe Ala Lys Phe Leu Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu  
100 105 110

Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr  
 115 120 125

Val Trp Leu Ser Ala Ile Trp Met Met Trp Tyr Trp Gly Pro Ser Leu  
 130 135 140

Tyr Ser Ile Val Arg Pro Phe Ile Gln Leu Leu Pro Ile Phe Phe Cys  
 145 150 155 160

Leu Trp Val Tyr Ile  
 165

<210> 51  
 <211> 669  
 <212> DNA  
 <213> artificial sequence

<220>  
 <223> Nucleotide sequence of Patient

<400> 51  
 aatcctcaca ataccgcaga gtctagactt cgtggtgact tctctcaatt ttctagggga 60  
 ccacccgtgt gtcttggcca aaattcgcag tccccaacct ccaatcactc accaacctct 120  
 tgtcctccaa tttgtcctgg ttatcgcctg atgtgtctgc ggcgttttat catatccctc 180  
 ttcatcctgc tgctatgcct catcttctta ttggttcttc tggattatca aggtatgttg 240  
 cccgtttgtc ctctaattcc aggatccaca acaaccagta cgggaccctg caaaacctgc 300  
 acgactcctg ctcaaggcaa ctctatgttt ccctcatggt gctgtacaaa acctacggat 360  
 ggaaattgca cmtgtattcc catcccatca tcttgggctt tcgcaaaata cctatgggag 420  
 tgggectcag tccgtttctc ttggttcagt ttactagtgc catttgttca gtggttcgta 480  
 gggctttccc ccaactgtttg gctttcagct atatggatga tattgtactg ggggccaaagt 540  
 ctgtacaaca tcttgagtcc ctttataccg ctgttaccaa ttttcttttg tctttgggta 600  
 tacatttaac ccctaacaaa acaaagagat ggggttatc cctgaatttc atgggttatg 660  
 taattggaa 669

<210> 52  
 <211> 181  
 <212> PRT  
 <213> artificial sequence

<220>

<223> Deduced sequence of DNA polymerase of Patient F

<220>

<221> MISC\_FEATURE

<222> (83)..(83)

<223> x = any amino acid

<400> 52

Ser Asn Leu Ser Trp Leu Ser Leu Asp Val Ser Ala Ala Phe Tyr His  
1 5 10 15

Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu Ile Gly Ser Ser  
20 25 30

Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Asn Ser Arg Ile His  
35 40 45

Asn Asn Gln Tyr Gly Thr Leu Gln Asn Leu His Asp Ser Cys Ser Arg  
50 55 60

Gln Leu Tyr Val Ser Leu Met Leu Leu Tyr Lys Thr Tyr Gly Trp Lys  
65 70 75 80

Leu His Xaa Tyr Ser His Pro Ile Ile Leu Gly Phe Arg Lys Ile Pro  
85 90 95

Met Gly Val Gly Leu Ser Pro Phe Leu Leu Val Gln Phe Thr Ser Ala  
100 105 110

Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser  
115 120 125

Tyr Met Asp Asp Ile Val Leu Gly Ala Lys Ser Val Gln His Leu Glu  
130 135 140

Ser Leu Tyr Thr Ala Val Thr Asn Phe Leu Leu Ser Leu Gly Ile His  
145 150 155 160

Leu Thr Pro Asn Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met  
165 170 175

Gly Tyr Val Ile Gly  
180

<210> 53  
 <211> 160  
 <212> PRT  
 <213> artificial sequence

<220>  
 <223> HBsAg Trans of Patient F

<400> 53

Pro Ile Cys Pro Gly Tyr Arg Trp Met Cys Leu Arg Arg Phe Ile Ile  
 1 5 10 15

Ser Leu Phe Ile Leu Leu Leu Cys Leu Ile Phe Leu Leu Val Leu Leu  
 20 25 30

Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Ile Pro Gly Ser Thr  
 35 40 45

Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Thr Pro Ala Gln Gly  
 50 55 60

Asn Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Thr Asp Gly Asn  
 65 70 75 80

Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Lys Tyr Leu  
 85 90 95

Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Phe Ser Leu Leu Val Pro  
 100 105 110

Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Ala  
 115 120 125

Ile Trp Met Ile Leu Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu Ser  
 130 135 140

Pro Phe Ile Pro Leu Leu Pro Ile Phe Phe Cys Leu Trp Val Tyr Ile  
 145 150 155 160

<210> 54  
 <211> 554  
 <212> DNA  
 <213> artificial sequence

<220>

<223> Nucleotide sequence of Patient G

<400> 54

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tccaatttgt cctgggtatc gctggatgtg tctgcggcgt tttatcatat tcctcttcat      60
cctgctgcta tgcctcatct tcttggttgg tcttctggac tatcaaggta tgttgcccgt      120
ttgtcctcta cttccaggaa catcaactac cagcacggga ccatgcaaga cctgcacgac      180
tcctgctcaa ggaacctcta tgtttccctc ttgttgctgt acaaaacctt cggacggaaa      240
ttgcacttgt attcccatcc catcgtcttg ggctttogca agattcctat gggagtgggc      300
ctcagtccgt ttctcttggc tcartttact agtgccattt gttcagtggg tcgtagggct      360
ttccccact gtttggtttt cagttatatt gatgatgtgg tattgggggc caagtctgta      420
caacatcttg aatccctttt tacctctatt accaattttc ttatgtcttt gggatacat      480
ttaaacccta agaaaaccaa acgttggggc tactccctta acttcatggg atatgtaatt      540
ggaagttggg gtac

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554

<210> 55

<211> 184

<212> PRT

<213> artificial sequence

<220>

<223> Deduced sequence of DNA polymerase of Patient G

<400> 55

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Ser Asn Leu Ser Trp Val Ser Leu Asp Val Ser Ala Ala Phe Tyr His
1           5           10           15

```

```

Ile Pro Leu His Pro Ala Ala Met Pro His Leu Leu Val Gly Ser Ser
          20           25           30

```

```

Gly Leu Ser Arg Tyr Val Ala Arg Leu Ser Ser Thr Ser Arg Asn Ile
          35           40           45

```

```

Asn Tyr Gln His Gly Thr Met Gln Asp Leu His Asp Ser Cys Ser Arg
50           55           60

```

```

Asn Leu Tyr Val Ser Leu Leu Leu Leu Tyr Lys Thr Phe Gly Arg Lys
65           70           75           80

```

```

Leu His Leu Tyr Ser His Pro Ile Val Leu Gly Phe Arg Lys Ile Pro
          85           90           95

```

Met Gly Val Gly Leu Ser Pro Phe Leu Leu Ala Gln Phe Thr Ser Ala  
100 105 110

Ile Cys Ser Val Val Arg Arg Ala Phe Pro His Cys Leu Ala Phe Ser  
115 120 125

Tyr Ile Asp Asp Val Val Leu Gly Ala Lys Ser Val Gln His Leu Glu  
130 135 140

Ser Leu Phe Thr Ser Ile Thr Asn Phe Leu Met Ser Leu Gly Ile His  
145 150 155 160

Leu Asn Pro Lys Lys Thr Lys Arg Trp Gly Tyr Ser Leu Asn Phe Met  
165 170 175

Gly Tyr Val Ile Gly Ser Trp Gly  
180

<210> 56  
<211> 160  
<212> PRT  
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Asp Tyr Gln Gly Met Leu Pro Val Cys Pro Leu Leu Pro Gly Thr Ser  
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Thr Thr Ser Thr Gly Pro Cys Lys Thr Cys Thr Thr Pro Ala Gln Gly  
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Thr Ser Met Phe Pro Ser Cys Cys Cys Thr Lys Pro Ser Asp Gly Asn  
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Cys Thr Cys Ile Pro Ile Pro Ser Ser Trp Ala Phe Ala Arg Phe Leu  
85 90 95

Trp Glu Trp Ala Ser Val Arg Phe Ser Trp Leu Xaa Leu Leu Val Pro  
100 105 110

Phe Val Gln Trp Phe Val Gly Leu Ser Pro Thr Val Trp Leu Ser Val  
115 120 125

Ile Leu Met Met Trp Tyr Trp Gly Pro Ser Leu Tyr Asn Ile Leu Asn  
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Pro Phe Leu Pro Leu Leu Pro Ile Phe Leu Cys Leu Trp Val Tyr Ile  
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aaactctgcw agatcccaga gtgagaggcc tgtatttccc tgctgggtggc tccagttcag	180
gaacagtaaa ccctgttccg acttctgtct ctcacacatc gtcaatcttc tgcaggattg	240
gggwcctgc gctgaacatg gagaacatca catcaggatt cctaggacct ctgctcgtgt	300
tacaggcggg gtttttcttg ttgacaagaa tcttcacaat accgcagagt ctagactcgt	360
ggtggacttc tctcaatttt ctagggggaa ctaccgtgtg tcttggccaa aattcgcagt	420
tcccaacctc caatcactca ccaacctcct gtctccaac ttgwcctggg tategctgga	480
tgtrtctgcg gcgttttatc atcttcctct tcatcctgct gctatgcctc atcttcttgt	540
tggttcttct ggactatcaa ggtatgttgc ccgtttgtcc tctarttcca ggatcttcaa	600
ccaccagcac gggaccatgc agaacctgca cgactcctgc tcaaggaamc tctatgaatc	660
cctcctgttg ctgtaccaa ccttcggacg gaaattgcac ctgtattccc atcccatcat	720

cctgggcttt cggaaaattc ctatgggagt gggcctcagc ccgtttctcc tgrctcagtt 780  
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tatggatgat gtgggtattgg gggccaagtc tgtaymgcat cttragtccc tttttaccgc 900  
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Arg Pro Val Phe Pro Cys Trp Trp Leu Gln Phe Arg Asn Ser Lys Pro  
50 55 60

Cys Ser Asp Phe Cys Leu Ser His Ile Val Asn Leu Leu Glu Asp Trp  
65 70 75 80

Gly Pro Cys Ala Glu His Gly Glu His His Ile Arg Ile Pro Arg Thr  
85 90 95

Pro Ala Arg Val Thr Gly Gly Val Phe Leu Val Asp Lys Asn Pro His  
100 105 110

Asn Thr Ala Glu Ser Arg Leu Val Val Asp Phe Ser Gln Phe Ser Arg  
115 120 125

Gly Asn Tyr Arg Val Ser Trp Pro Lys Phe Ala Val Pro Asn Leu Gln  
130 135 140

Ser Leu Thr Asn Leu Leu Ser Ser Asn Leu Xaa Trp Leu Ser Leu Asp  
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Val Ser Ala Ala Phe Tyr His Leu Pro Leu His Pro Ala Ala Met Pro  
165 170 175

His Leu Leu Val Gly Ser Ser Gly Leu Ser Arg Tyr Val Ala Arg Leu  
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Ser Ser Xaa Ser Arg Ile Phe Asn His Gln His Gly Thr Met Gln Asn  
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Leu His Asp Ser Cys Ser Arg Xaa Leu Tyr Glu Ser Leu Leu Leu Leu  
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Tyr Gln Thr Phe Gly Arg Lys Leu His Leu Tyr Ser His Pro Ile Ile  
225 230 235 240

Leu Gly Phe Arg Lys Ile Pro Met Gly Val Gly Leu Ser Pro Phe Leu  
245 250 255

Leu Xaa Gln Phe Thr Ser Ala Ile Cys Ser Val Val Arg Arg Ala Phe  
260 265 270

Pro His Cys Leu Ala Phe Ser Tyr Met Asp Asp Val Val Leu Gly Ala  
275 280 285

Lys Ser Val Xaa His Leu Xaa Ser Leu Phe Thr Ala Val Thr Asn Phe  
290 295 300

Leu Leu Ser Leu Gly Ile His Leu Asn Pro Xaa Lys Thr Lys Arg Trp  
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Thr Pro Leu Ser Pro Pro Leu Xaa Asn Thr His Pro Gln Ala Met Gln  
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Trp Asn Ser Thr Thr Phe His Gln Thr Leu Xaa Asp Pro Arg Val Arg  
35 40 45

Gly Leu Tyr Phe Pro Ala Gly Gly Ser Ser Ser Gly Thr Val Asn Pro  
50 55 60

Val Pro Thr Ser Val Ser His Thr Ser Ser Ile Phe Ser Arg Ile Gly  
65 70 75 80

Xaa Pro Ala Leu Asn Met Glu Asn Ile Thr Ser Gly Phe Leu Gly Pro  
85 90 95

Leu Leu Val Leu Gln Ala Gly Phe Phe Leu Leu Thr Arg Ile Leu Thr  
100 105 110

Ile Pro Gln Ser Leu Asp Ser Trp Trp Thr Ser Leu Asn Phe Leu Gly  
115 120 125

Gly Thr Thr Val Cys Leu Gly Gln Asn Ser Gln Phe Pro Thr Ser Asn  
130 135 140

His Ser Pro Thr Ser Cys Pro Pro Thr Xaa Pro Gly Tyr Arg Trp Met  
145 150 155 160

Xaa Leu Arg Arg Phe Ile Ile Phe Leu Phe Ile Leu Leu Leu Cys Leu  
165 170 175

Ile Phe Leu Leu Val Leu Leu Asp Tyr Gln Gly Met Leu Pro Val Cys  
180 185 190

Pro Leu Xaa Pro Gly Ser Ser Thr Thr Ser Thr Gly Pro Cys Arg Thr  
195 200 205

Cys Thr Thr Pro Ala Gln Gly Xaa Ser Met Asn Pro Ser Cys Cys Cys  
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Thr Lys Pro Ser Asp Gly Asn Cys Thr Cys Ile Pro Ile Pro Ser Ser  
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Trp Ala Phe Gly Lys Phe Leu Trp Glu Trp Ala Ser Ala Arg Phe Ser

245

250

255

Xaa Leu Ser Leu Leu Val Pro Phe Val Gln Trp Phe Val Gly Leu Ser  
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Pro Thr Val Trp Leu Ser Val Ile Trp Met Met Trp Tyr Trp Gly Pro  
275 280 285

Ser Leu Tyr Xaa Ile Leu Ser Pro Phe Leu Pro Leu Leu Pro Ile Phe  
290 295 300

Phe Cys Leu Trp Val Tyr Ile  
305 310

a

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>												
Int. CL <sup>7</sup> : C12N7/00, 15/01, 15/36, 15/51, C12Q1/70												
According to International Patent Classification (IPC) or to both national classification and IPC												
<b>B. FIELDS SEARCHED</b>												
Minimum documentation searched (classification system followed by classification symbols) SEE BELOW												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SEE BELOW												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPIDS, MEDLINE, CA. KEYWORDS: Hepatitis B/Nucleotide/Nucleoside/Resistan?/Muta?/Adefovir/ Lamivudine/Tenofivir/Thiacydidine/HBsAg/Polymrase and similar terms												
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
X	WO 01/94559 (Melbourne Health) 13 December 2001  Claims, p.12-19, p.22 line 25- p.24 line 25, and p. 25 line 30 - p. 26 line 9	1-125, 169-202										
X	WO 01/57244 (Melbourne Health) 9 August 2001  Claims, Table 1, p. 17 line 7 - p. 21 line 12 and p. 25 line 16 - p. 33 line 2	1-17, 19-74, 80, 86, 95, 106, 119, 123-127										
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&amp;" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 27 May 2003		Date of mailing of the international search report 06 JUN 2003										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929		Authorized officer  <b>ALISTAIR BESTOW</b> Telephone No : (02) 6283 2450										

**Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos : 126, 159, 160 (completely), 161-168 (partially)  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
The claims are not restricted to the technical features of the invention, namely hepatitis B variants, methods of using these variants and products of these methods.  
Claims 161-168 have only been searched in so far as they relate to HBV nucleic acid or peptides sequences, antibodies, ribozymes and antisense that are capable of inhibiting the variant HBVs of the invention
3. ☐ Claims Nos :  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

**Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box for summary inventions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/21317 (Western Health Care Network) 22 May 1998  Claims, p. 4 line 5 - p. 7 line 12 and p. 8 line 28 - p. 11 line 20,	1-17, 19-37, 39, 40, 42-50, 54, 55, 58-74, 76-78, 80-90, 94, 95, 98, 100-114, 118, 119, 122, 170- 178, 180-182, 184-186, 190, 194-202
X	Yeh, C. et al., 2000, <i>Clearance of the original hepatitis B virus YMDD-motif mutants with emergence of distinct lamivudine-resistant mutants during prolonged lamivudine therapy</i> , Hepatology, 31:1318-1325  See whole document	1-17, 19-37, 39, 40, 49, 50, 54, 55, 58-74, 76, 77, 78, 82, 85, 86, 89, 90, 94, 95, 98, 100-102, 106, 109, 113, 114, 118, 119, 122, 127-129
X	Seigneres, B. et al., 2000, <i>Evolution of Hepatitis B virus polymerase gene sequence during famciclovir therapy for chronic hepatitis B</i> , Journal of Infectious Diseases, 181:1221-33  See whole document	1-17, 19-38, 42, 50, 54, 57, 58-74, 80, 85, 86, 90, 97, 104, 109, 110, 114, 118, 121, 122, 127-129
X	Ogata, N. et al., 1999, <i>Novel patterns of amino acid mutations in the hepatitis b virus polymerase in association with resistance to lamivudine therapy in japanese patients with chronic hepatitis B</i> , Journal of Medical Virology, 59:270-276  See whole document	1-17, 19-37, 43, 59-74, 81, 105
X	Bock, C. et al., 2002(February), <i>Selection of hepatitis B virus polymerase mutants with enhanced replication by lamivudine treatment after liver transplantation</i> , Gastroenterology, 122:264-273  See whole document	1-17, 19-37, 39, 44, 54, 55, 58-74, 83, 94, 95, 98, 100, 107, 118, 119, 122



C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>Cane, P. et al., 1999, <i>Analysis of hepatitis B virus quasispecies changes during the emergence and reversion of lamivudine resistance in liver transplantation</i>, Antiviral Therapy, 4:7-14</p> <p>See whole document</p>	1-17, 19-37, 39, 43, 45, 49, 50, 55, 58-74, 81, 84, 86, 89, 90, 94, 95, 98, 100, 102, 108, 110, 113, 114, 118, 119, 122

**Supplemental Box**

(To be used when the space in any of Boxes I to VIII is not sufficient)

**Continuation of Box No II:**

Invention 1: Claims 1- 20, 38, 59-75, 99, 123-125, 127, 130-134, 170, 178, 179, 195 (all partially) relating to an isolated Hepatitis B virus (HBV) variant comprising a mutation in a gene encoding DNA polymerase resulting in an amino acid addition, substitution and/or deletion at amino acid position rt21 of the HBV DNA polymerase, the use of these variants, and methods for determining whether a HBV variant exhibits decrease sensitivity to anti-viral agents or reduced interactivity to an antibody to HBV surface antigen.

Invention 2: 1- 20, 38, 59-75, 77, 99, 101, 123-125, 127, 130-134, 136, 170, 178, 179, 181, 195 (all partially) relating to an isolated HBV variant comprising a mutation in a gene encoding DNA polymerase resulting in an amino acid addition, substitution and/or deletion at amino acid position rt122 of the HBV DNA polymerase, the use of these variants, and methods for determining whether a HBV variant exhibits decrease sensitivity to anti-viral agents or reduced interactivity to an antibody to HBV surface antigen.

Inventions 3-37: relating to HBV variants comprising a mutation in a gene encoding DNA polymerase and/or HBsAg resulting in an amino acid addition, substitution and/or deletion at amino acid positions rt124, rt28, rt130, etc, rt251 or the equivalent position in the overlapping HBsAg, the use of these variants, and methods for determining whether a HBV variant exhibits decrease sensitivity to anti-viral agents or reduced interactivity to an antibody to HBV surface antigen.

The common feature linking the group of inventions resides in the elucidation of the link between reduced sensitivity to anti-HBV agents such as ADV, LMV, FTC and TFV and mutation of the nucleotide sequence encoding HBV DNA polymerase or the overlapping S gene (HBsAg). However, this is already known in the art (see Chen et al., 1999, Human hepatitis B virus mutants: significance of molecular changes, FEBS Letters, 453:237-242, and citations below), as such the claims relate to multiple inventions, *a posteriori*.

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
WO	200194559	AU	20008109	AU	200163672	EP	1297109
WO	200157244	AU	200131415	EP	1257661		
WO	9821317	AU	37628/97	EP	964916	US	6555311
							END OF ANNEX

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